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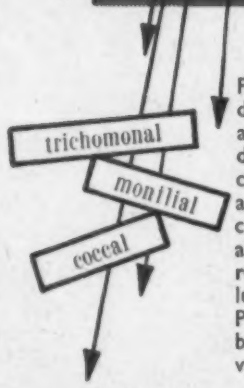

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LONDON SATURDAY SEPTEMBER 26 1959

NUCLEIC ACIDS AND THEIR ROLE IN FUTURE CHEMOTHERAPY OF TUMOURS AND VIRUS DISEASES*

BY

Sir ALEXANDER TODD, F.R.S.

Professor of Organic Chemistry, University of Cambridge

It is my intention in this lecture to review some of our present knowledge about the connexion between nucleic acids, viruses, and cancer, to consider this in the light of our understanding of nucleic acid chemistry, and to see whether any conclusions can yet be reached about the course of future chemotherapeutic work in the fields of cancer and virus diseases. I wish to make it abundantly clear that I speak as a chemist whose interests have lain in the structural chemistry of the nucleic acids; I am in no sense a biologist, and my only claim to speak on this subject rests on my belief that we have now reached a stage in which the chemist must bring his experience and outlook to bear on these vital problems, as well as the biologist, the medical scientist, and the physicist. Only by the joint effort of all can we pass through the present phase of searching in a haystack of complexities and emerge with the needle of true understanding of what may well be some of life's innermost secrets. But in the present circumstances I am well aware that the task I have set myself is not an easy one, for there is much conflicting evidence and much that we do not know. Moreover, my discussion may well be coloured somewhat by my personal and professional prejudices and my very incomplete knowledge of the biological aspects of the subject. I can only hope that my attempted synthesis may be of some interest and value, at least to the non-specialist.

Chemical Nature of Genes

One of the most striking and important recent advances in genetics has been the recognition of the chemical nature of the genes or units of heredity. During the second decade of this century it was recognized by the geneticists that the genes are carried in the chromosomes. These latter are composed of deoxyribonucleic acid (D.N.A.) and protein combined in some way not yet wholly understood, and it was for many years believed that genetic specificity was associated entirely with the proteins of the living cell. Attention first became focused on the nucleic acids as genetic material as a result of a series of studies starting with the observation of Griffith (1928) that he could transform one specific S-type pneumococcus into another specific S-type by injecting non-virulent R-forms into mice together with large amounts of heat-killed S-pneumococci of a type other than that of the organism from which the R-cells were derived. Living virulent S-organisms of the same type as the heat-killed S-forms were then recovered from the animals.

*The first Jephcott Lecture, delivered at the Royal Society of Medicine, London, on May 27, 1959.

Later on, other workers found that the addition of an extract of one type of capsulated pneumococcus to a culture of a non-capsulated rough form would convert the latter into the same type of capsulated organism which provided the extract. Finally, Avery, McLeod, and McCarty (1944) showed that the substance in these extracts responsible for this effect was D.N.A. All subsequent work has confirmed that the primary genetic material in this organism is D.N.A. The evidence in higher forms of life than bacteria is perhaps not so clear-cut despite the interesting experiments of Benoit, Leroy, Vendrely, and Vendrely (1957a, 1957b, 1958), but it is at least now widely accepted as a working hypothesis that the primary genetic material is D.N.A. So far as I am aware, we do not know any facts which contradict this hypothesis.

Further evidence for the role of nucleic acids in genetic continuity comes from the study of viruses. Whether viruses are to be regarded as "living" or not is a matter for academic debate, and we can leave it on one side for the moment. But at least there is a close similarity between genes and viruses, and, indeed, when one considers the results of transduction experiments in *Salmonella* using a bacterial virus (Zinder and Lederberg, 1952), the difference between the two appears negligible. In the phages or bacterial viruses the evidence is very strong that genetic continuity resides in the D.N.A. In these materials infection of the host cells is accomplished through injection of phage D.N.A.; the protein coat remains outside and at most only very small amounts of protein enter the host.

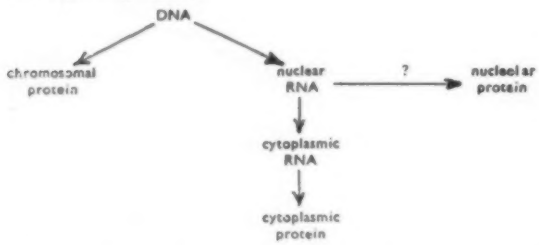
Although quite a number of viruses other than bacteriophages are known which contain D.N.A. and protein—that is, are deoxyribonucleoproteins—many others, including some of the most thoroughly investigated plant viruses, are ribonucleoproteins. Particularly striking observations have been made which show that it is the ribonucleic acid (R.N.A.) component which is responsible for genetic continuity in tobacco mosaic virus. In this case the virus particle itself is a hollow cylinder of protein material, the R.N.A. being embedded in the hollow central portion. Both Fraenkel-Conrat (1956) and Gierer and Schramm (1956) have separated the R.N.A. from the protein of tobacco mosaic virus and shown that the infectivity is carried by the R.N.A. and not by the protein, although recombination of the R.N.A. and protein gives a more infective material than the protein-free R.N.A. More striking still are Fraenkel-Conrat's observations that if the R.N.A. of one strain of virus is combined with the protein

component of another the nucleoprotein so produced is infective, but on infection it is the nucleoprotein—that is, virus—corresponding to the R.N.A. component that is exclusively produced. Somewhat similar observations have been made with other R.N.A.-containing viruses.

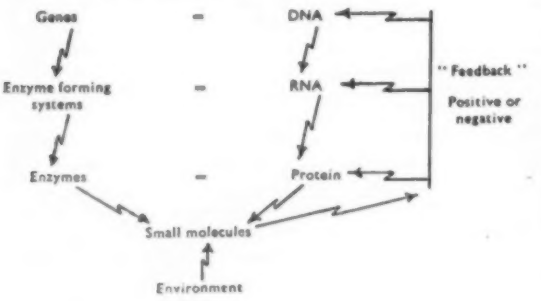
The evidence available, then, shows clearly that nucleic acids can and do act as genes or carriers of genetic information, and it is at least highly probable that they do so in all forms of living matter and in the viruses. In living cells the primary carriers of the information—the hereditary nuclear genes—are almost certainly the D.N.A.s. These D.N.A. molecules are not part of the dynamic pool of metabolites in cells. Studies with radioisotopic tracers have shown that they do not lose their isotopic constituents once they are incorporated and the precursors are incorporated only when new D.N.A. is being synthesized, normally at the time of cell division. The D.N.A. has indeed an astonishing degree of metabolic inertness and is in this sense quite unlike any other type of organic molecule in the cell. R.N.A. can clearly provide genetic continuity in the viruses, but in living cells it seems to occupy a lower place than D.N.A., being in some way controlled by the latter just as the R.N.A. itself controls protein synthesis, and being further subject to much more rapid synthesis and turnover.

Interaction of Nucleic Acids and Protein

The relationships between D.N.A., R.N.A., and protein, and the way in which control of the one by the other is exercised, are matters to which one could devote not one, but several lectures, and I shall confine myself here to giving a very simple—and, no doubt, oversimplified—picture which seems to me to be in accord with the bulk of our present knowledge, and which I accept as a working hypothesis. It is given by the following scheme:



A somewhat more elaborate and more comprehensive picture of cellular economy due to Potter (1957, 1958) is given below. It emphasizes the interaction of genes and environment through "feed-back" mechanisms which form part of the overall control of growth and normal functioning of the living cell.



These facts and views on the genetic importance of the nucleic acids have an obvious relevance to the cancer problem, and from them stem two of the main current hypotheses on which approaches to cancer and virus chemotherapy are based. These are the deletion hypothesis, which has been clearly expounded in publications by Potter (1957, 1958), and the attractive virus hypothesis discussed by Stanley (1958). According to the former, one must think of normal cells undergoing mutations leading to the loss of the negative feed-back systems which keep in check the specific enzymes needed for cell division and the synthesis of D.N.A., the deletion of some specific D.N.A. molecules necessary for surface protein production, and of katabolic enzyme formation (through deletion of R.N.A. enzyme-forming systems).

The mutations triggering off the process might be a result of inherent random errors in nucleic acid replication, errors brought about by action of carcinogens or radiation damage, or loss of certain enzyme systems which fail to replicate fast enough during cell division, a situation which might arise through competition with a viral infection or by combination with carcinogens such as azo-dyes. Any or all of these may be involved in the different types of cancer. The virus theory would seek to explain all types of cancer (other than the present generally accepted virus cancers) by the intervention of viruses present in cells, but which are inactive or non-virulent until stimulated or modified either by external conditions, by carcinogens or radiation, or presumably also by random mutation. It seems to me, at least, that there is really less difference between these hypotheses than might at first sight appear. Both depend on mutation in nucleic acids and differ essentially in how the cancer process starts; perhaps a good deal depends, too, on one's definition of a virus. One thing seems clear—the two hypotheses lead to essentially similar approaches to cancer chemotherapy, Everything comes back finally to nucleic acid.

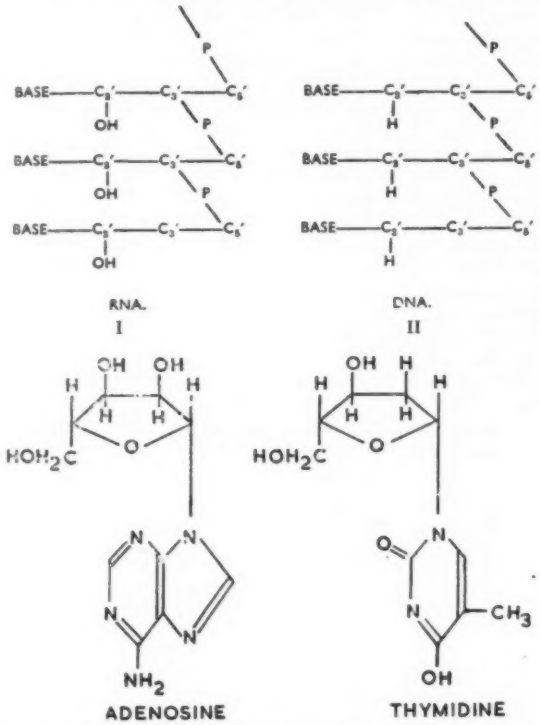
Having now cleared the ground by indicating in a general way the facts about genetic control by nucleic acids, we must consider what these materials are, and how they can act as carriers of information. Here there is available a moderate amount of fact and a very large amount of speculation. Much of the speculation is reasonable, but there has been a tendency at times to forget that it is speculation and that much more experimental work is needed before we can feel sure about the details of nucleic acid function.

Chemical Structure of Nucleic Acids

It is now just under eight years since the general theory of the chemical structure of the nucleic acids was announced by Brown and Todd (1952, 1955), based on an exhaustive study of the chemistry of the simple nucleosides and nucleotides and the hydrolytic behaviour of the two types of nucleic acid (D.N.A. and R.N.A.) found in nature. According to the theory, which is now firmly established, both types are polydiesters of phosphoric acid, built up by polycondensation of many individual nucleotide units to give linear polynucleotides with a regular recurring 3′:5′-internucleotidic linkage. The ribopolynucleotides can be represented diagrammatically as I and the deoxyribopolynucleotides as II.

The individual nucleosides are N-β-glycosides of heterocyclic bases of the purine or pyrimidine series, the

sugar being D-ribofuranose in the case of the R.N.A.s, and 2-deoxy-D-ribofuranose in the D.N.A.s. Typical examples are adenosine (adenine 9-β-ribofuranoside) and thymidine (thymine 3-β-2′-deoxy-D-ribofuranoside). It seems that most R.N.A.s contain only four simple nucleosides (adenosine, guanosine, uridine, and cytidine), and the very interesting discovery in recent years that some preparations of R.N.A.s from various natural sources contain traces of other " unnatural " nucleosides is probably an indication that very small amounts of other nucleic acids with a composition quite different



from the common ones do occur alongside them in some cells. The D.N.A.s yield four main nucleotides (deoxyadenosine, deoxyguanosine, deoxycytidine, and thymidine), together with two less frequent components (5-methyldeoxycytidine and 5-hydroxymethyldeoxycitidine), and in this series, too, trace constituents occur in some natural materials. Variable estimates have been given for the molecular weights of the natural materials ; although they may be subject to error, values of about 2 million to 15 million are frequently quoted. Whatever the accuracy of these determinations may be, it is clear that we are dealing here with very long polynucleotide chains, and that, even with as few as four monomeric units, a fantastic number of individual nucleic acids is possible, each differing from the other in the sequence of nucleoside residues.

Self-replicating Systems

Following on the chemical work in nucleic acid structure, it was possible to interpret the *x*-ray diagrams of D.N.A. obtained by Wilkins (1956) and others, and this led to the realization that D.N.A. normally exists as a double molecule in which two polynucleotide chains combine to form a double helical structure with the sugar and phosphate on the outside and the bases in the core of the helix lying at right angles to the main axis (Fig. 1). Watson and Crick (1953) were now able to make their brilliant contribution by suggesting the reason for the existence of the D.N.A. double helix, and at the same time to reveal how D.N.A. could form

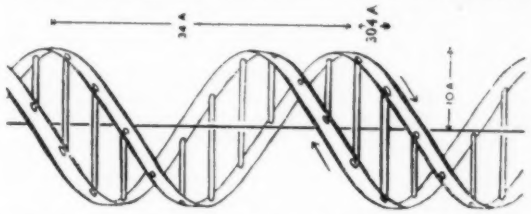


FIG. 1.—Diagrammatic representation of the D.N.A. double helix. The ribbon-like helices are made up of the sugar residues linked by phosphate groups, and the horizontal rods represent the paired bases.

a self-replicating system. They drew attention to the fact that analyses of a large number of D.N.A. samples from different sources showed that, taking the four main bases present in the nucleosides, the ratio of adenine to thymine was 1:1 and of guanine to cytosine 1:1, although this was far from true for the ratios of other pairs—for example, adenine to guanine. They suggested that this was due to specific hydrogen bonding between these pairs of bases, and that it was this specific bonding between the bases which held the double helix together (Fig. 2).

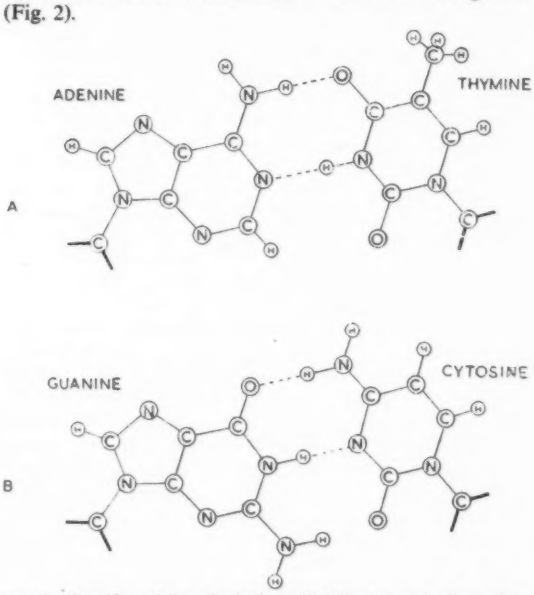
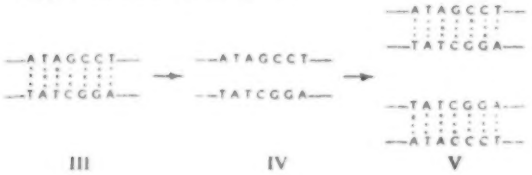


FIG. 2.—Specific pairing of adenine with thymine and of guanine with cytosine.

Although it cannot be said that the Watson–Crick theory has been completely verified, I think that all evidence obtained since its promulgation is so much in its favour that it can be regarded as correct in its essentials. Particularly striking in this connexion are the enzymic syntheses of D.N.A. by Adler *et al.* (1958) ; Bessman *et al.* (1958a, 1958b) ; Schachman *et al.* (1958). The observation by Kernberg and his colleagues that an existing D.N.A. molecule will grow in the presence of the appropriate enzyme and a mixture of the four nucleoside triphosphates, but will add only one or two residues when one nucleoside triphosphate alone is used, is precisely what one would

expect on the Watson–Crick theory of specific base pairing and is hard to explain otherwise.

The replication theory of Watson and Crick can be simply explained in the following way. If we describe the four main deoxynucleosides by the initial letters of their trivial names—that is, A, G, T, and C—and we assume that in the double helix of D.N.A. the pairing of A with T and of G with C is obligatory, then the expression (III) could represent part of a D.N.A. molecule, the sequence in each polynucleotide chain being determined by the other.



III IV V

If we imagine the two strands of the helix to separate as in IV and to be in a medium where D.N.A. synthesis is occurring, each of the separated chains will build upon itself the complementary chain giving, as in V, two double helices of D.N.A., each identical with the original (III). This furnishes a beautiful illustration of the way in which D.N.A. may provide genetic continuity in a cell, for, if on division even one strand of D.N.A. is passed on, the progeny must continue to reproduce D.N.A. of the original parental pattern.

It is generally believed that nuclear D.N.A. acts as a kind of template for the synthesis of R.N.A.—and also for chromosomal protein—and it seems that the R.N.A. produced also forms a self-replicating system. True, isolated R.N.A. does not seem to exist normally in a double helical form, but the same base-pairing rules should apply in R.N.A. as in D.N.A.—that is, adenine with uracil and guanine with cytosine—and even in D.N.A. it is the single strands which are active in the replication process. The stable double helical form, although appropriate to the inert D.N.A., would hardly be expected in the very active R.N.A. It will be recalled in this connexion that polyribonucleotides synthesized by means of the Ochoa enzyme (polynucleotide phosphorylase) (Grunberg-Manago and Ochoa, 1955) can form two-stranded and even three-stranded helical structures under certain conditions, although under others they exist as single-stranded random coils.

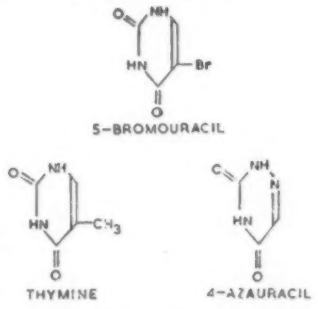
These views about the manner in which nucleic acids can be regarded as self-replicating systems, even if they are oversimplified in some respects, do provide an explanation of mutations. Any change which will destroy the base-pairing pattern, even at one point in the molecule, would be enough to alter the hereditary characteristics—that is, to bring about mutation. Equally, interference with the base-pairing or rupture of the polynucleotide chain might in theory provide a means of destroying a virus or rendering it harmless. And it is on this knowledge, incomplete though it is, that any rational approach to the chemotherapy of virus disease, and also, I believe, of cancer, must ultimately be based at the present time. Although I believe that the virus and cancer problems are very closely related, it is convenient to consider them briefly in turn.

It is through immunology that the major contributions to the control of virus diseases have been made, and I have no doubt that vaccine therapy will continue to be of great importance. But at the same time our increasing knowledge of the nucleic acids and the real nature of viruses may well lead to a refinement of immunological methods resulting in more effective agents with very high specificity in their action. However, I do not propose to discuss the immunological aspects of virus and tumour therapy, and will confine myself to the approaches related to chemotherapy in the usually understood sense of the term.

Therapeutic Lines of Attack on Virus Diseases

Treatment of virus infections with a large variety of chemical agents has been tried in the past, but relatively little success has been recorded. Apart from some positive effects with antibiotics, the significance of which in our present context I find difficult to assess, most of the meagre positive results seem to have come from the use of substances related to pyrimidine and purine, in which there would seem to be a possibility of incorporation of the drug molecules into the virus polynucleotide, thereby destroying its replication properties, or of interfering—possibly by competitive inhibition—with the synthesis of the natural nucleosides or nucleotides. As an example, I would recall to your attention experiments carried out by Matthews and Smith (1955) and Matthews (1957), who achieved some measure of protection against the cucumber virus by prior spraying of the plants with 8-azaguanine. This effect was plausibly believed to be due to incorporation of the latter substance into the R.N.A. of the rapidly proliferating virus.

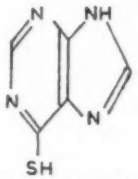
In the same way, there is evidence that other purine and pyrimidine antagonists—for example, 4-azauracil, 4-azathymine, 5-bromouracil, 5-fluorouracil—can be incorporated into nucleic acids *in vivo*. Of course, it is not necessary that such agents must be incorporated into nucleic acid in order to be active, nor, strictly speaking, can we say that where they are incorporated it is the production of the abnormal nucleic acid which is the direct cause of the observed action on the virus. The chemotherapeutic agents may—and in, for example, the case of 5-fluorouracil and 6-mercaptopurine do—act by being antimetabolites for the synthesis of a precursor (thymine in the fluorouracil case) of the nucleic acids. Incorporation might then, in some cases at least, be secondary in importance, but it is an attractive and wholly reasonable aim to seek to destroy a virus by making it incorporate into its nucleic acid component some unnatural bases or nucleosides which would necessarily upset its replication.



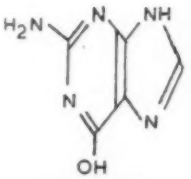
From this standpoint, I would suggest that instead of the simple purine and pyrimidine analogues which have so far been used it might be desirable to try the effect of small synthetic oligonucleotides containing in them abnormal nucleotides—including those modified in the sugar or phosphate residues as well as those with unnatural base components. Evidence from the investigations of Ochoa and others on polynucleotide

phosphorylase seem to show that the purified enzyme needs an oligo- or poly-nucleotide primer. This suggests that oligonucleotides might well serve as much better starting-points for R.N.A. synthesis in the cell than a single base or nucleoside, and that such compounds might therefore be better as therapeutic agents.

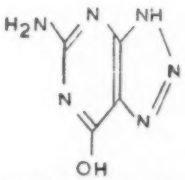
Mutations might well be brought about or total inactivation of a virus achieved by modification of the



6-MERCAPTOPURINE



GUANINE



8-AZAGUANINE

virus nucleic acid by chemical reagents which attack and modify individual groups in the nucleotide units. Thus Schuster and Schramm (1958) and Gierer and Mundry (1958a, 1958b) showed that nitrous acid, which deaminates adenosine, guanosine, and cytosine residues, could, according to the conditions, mutate or totally inactivate the R.N.A. of tobacco mosaic virus—and it appears that the protein coat of the virus is permeable to nitrous acid, since the effects can be produced on intact virus particles. The demonstration of mutation by this means is particularly interesting, since radiation or other chemical agents usually produce only total inactivation when they attack the virus. Nitrous acid is not a very discriminating reagent and is not, therefore, likely to have any practical value, but it is interesting that the protein does not protect the infective nucleic acid from attack by small molecules. Against larger molecules there may be protection, but, as the viral R.N.A. seems to separate from the protein coat in the initial stages of infection and multiply in the nucleus, the possibility of chemical attack on the nuclear, and presumably unprotected, R.N.A. remains.

Another possible chemical line of attack might be to use synthetic polymers with the object of blocking the virus polynucleotide chains by attachment either through covalent or hydrogen bonds, so as to prevent polynucleotide synthesis on the virus template. Little work has been done on this approach as yet, but the interesting experiments of Allfrey and Mirsky (1958), in which he was able to show that replacement of a large proportion of the D.N.A. in cell nuclei by a number of anionic polyelectrolytes, such as polyethylene sulphonate, heparin, and chondroitin sulphate, allowed the nuclei to continue much of their normal biochemical activity, suggest that possible therapeutic agents of this type are worthy of serious consideration.

The various types of approach to a chemotherapy of virus diseases are all under examination in greater or less degree, and are thus not to be regarded as novel. But, although I believe they are likely to form in one guise or another the basis for further developments, we need a good deal more information about the viruses and their nucleic acids before these developments can be made on a truly rational basis. It is important, therefore, to consider at least the major gaps in knowledge which are baffling the chemists. In the first place, of course, the methods discussed rest on preventing the multiplication of viral nucleic acids. But they are applicable to any nucleic acid and not specific to viral nucleic acid, so that success really depends on an assumption that synthesis of viral nucleic acid can be stopped and the virus inactivated before serious damage is done to the nucleic acids of the host cell.

Now it is by no means impossible that this could be done, although it has to be remembered that there are certain cells in any living organism which are rapidly dividing and in which vigorous nucleic acid synthesis is going on; there is an obvious danger that these may be seriously damaged as well as the virus. If we are to avoid this danger, we must find out in more detail the peculiarity in the nucleotide sequence or composition of the virus polynucleotides—for some special feature they must surely have to explain their capacity to impose themselves so successfully on the economy of the host cells. It is difficult to see how we can reach the desired specificity in a chemotherapeutic agent (other than by pure chance) unless this kind of information is first obtained.

Cancer Chemotherapy

The same kinds of considerations apply to the problem of cancer chemotherapy. It is in one sense a problem more complex and in another simpler than that of the orthodox virus diseases. It is simpler only in the sense that in the early stages it may be more localized and that destruction of complete cells rather than one constituent in them would usually be a satisfactory solution. But, of course, the great difficulty of administering an agent to kill rapidly proliferating tumour cells without killing other rapidly proliferating cells—for example, in bone marrow—remains. This difficulty has gravely hampered investigations in this field, since if the agent is designed to interfere with nucleic acid synthesis or replication, then either a very high specificity is required or some means must be found of localizing the effect of the drug. Of course, if we recall the "deletion hypothesis" of Potter, mentioned earlier, in which the loss of the feed-back system of control is regarded as the primary feature of a tumour cell, it should be possible to attack the tumour cell at the level of its enzyme proteins rather than at the nucleic acid level and still achieve success.

Methods based on this general theory have been, and are being, applied, and promising results are being obtained. Thus the work of Bergel *et al.* (1957) on xanthine oxidase in tumour therapy is of very great interest, as well as other efforts to work with enzyme systems in which there seems to be at least a quantitative difference between normal and tumour cells; similarly, work on abnormal amino-acids—for example, fluorophenylalanine—aimed at interference with protein synthesis has given some interesting results. But from the nucleic acid viewpoint—since ultimately the problem is bound up with the activity of one or more nucleic acids of abnormal type (without going into the question of their origin)—broadly speaking, methods similar to those mentioned above in connexion with virus diseases are the ones most likely to be followed. They have indeed been followed consciously or unconsciously, as

can be seen from the work on 6-mercaptopurine or 5-fluorouracil, and on the so-called mutagenic agents, to name only a few agents of promise. In the tumour problem, as with the viruses, however, we lack vital knowledge about the nucleic acids of the cell.

What are the significant differences between the nucleic acids of the tumour cell and those of the normal cell? Differences there must be, but I am sure they are not likely to be determined on the basis of gross analysis of cellular nucleic acid preparations as we now know them. For surely there must be many different nucleic acids in the nucleus of an animal cell, and the abnormality of the tumour cell is not *a priori* likely to be noticed in an analysis of the mixture for purine and pyrimidine bases. The vital difference may lie only in base sequence of a few of the nucleic acids present, although there is another possibility which should perhaps be borne in mind. In the last year or two there have been a number of discoveries of very small amounts of abnormal bases and nucleosides in hydrolysates of many natural nucleic acids. Since these preparations were doubtless heterogeneous (it is doubtful whether a homogeneous nucleic acid has yet been prepared), it seems to me that instead of these abnormal nucleosides being present as very widely spaced units in a long polynucleotide chain they may well represent residues from nucleic acids of quite unusual structure which are present as very minor components of the nucleic acid preparations examined. If this is so, is it possible that these minor components are important in the economy of the cell? Such questions—and they are important questions—we cannot answer until we can separate and study the nucleic acids as homogeneous individuals.

Conclusion

To sum up, then, it seems to me that the future progress of chemotherapeutic work based on nucleic acids in the tumour and virus field, if it is to be something other than a hit-and-miss procedure, depends on real physical and chemical advances being made in two main directions. Firstly, methods must be found—and they do not exist to-day—for separating into their individual components the nucleic acids of cells and of preparing pure individual nucleic acids: this may first be attained with the nucleic acids of some of the plant viruses. Secondly, we must perfect experimental methods which will allow us to study the structure of these pure nucleic acids in detail and clarify their relationship with one another. Given these advances, we would not have an immediate solution to the problems we have been discussing, but without them I find it hard to be hopeful about quick results in virus chemotherapy. For we are dealing here with a branch of chemotherapy which demands agents of a remarkable specificity which has so far been observed only in immunological studies.

It is this need for a very high degree of specificity, coupled with the need for complete and irreversible inactivation of certain polynucleotides, that makes the problem of virus and tumour disease so intractable. But the progress so far made in their treatment with chemical agents suggests that, with the further development of basic knowledge of nucleic acid structure and function, the combined work of the chemist and biologist will in the future yield a real solution of these vital problems.

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CONTROL OF ADRENAL SECRETION OF ELECTROLYTE-ACTIVE STEROIDS*

ADRENAL STIMULATION BY CROSS-CIRCULATION EXPERIMENTS IN CONSCIOUS SHEEP

BY

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PART II

In the light of the evidence that local changes of adrenal ionic environment were not sufficient to account for the changes of electrolyte-active steroid secretion which occur during change of Na^+ balance, two possibilities existed: (1) Other non-hormonal changes at the adrenal level were operative and, in combination with the ionic factors outlined above, were sufficient to cause alterations of adrenal secretion seen during change of sodium balance. (2) That a hormonal stimulus was acting upon the adrenal from a distance. In view of the fact that the transplanted adrenal gland is almost certainly denervated, the stimulus would be humoral, not neural.

It will be recognized readily, in relation to the many physiological factors which change in Na^+ depletion, that the way is open to induce many combinations of change at the adrenal level. Apart from infusions of

*Part I appeared in last week's issue.

pharmacologically active agents such as acetylcholine, noradrenaline, serotonin, and bradykinin, changes of blood flow can be induced by application of cuffs to the two carotid loops—for example, inflation of both cuffs to 200 mm. Hg reduces blood pressure in the head and increases it systemically as a result of the carotid sinus reflex. The cuff on the transplant loop may be placed either cranial or caudal to the adrenal so that the gland is included in either the high- or low-pressure section of the animal's systemic circulation. These blood-flow changes can be combined with concurrent ionic changes. Some experiments have been made, but the work has not progressed yet to a point permitting any conclusion. We wish to report here work on the second possibility.

Arterial Cross-circulation Experiments in Conscious Sheep

In endeavouring to find out whether such a hormonic agent existed, it seemed correct formally to try first *to demonstrate it in the circulating* blood rather than seek it in excreta or make an extract of a supposed site of origin. For the reasons stated already, the aim would be to make such experiments in conscious confident animals. To this end we have engaged in arterial cross-circulation experiments in conscious sheep. As a working hypothesis, and by analogy with corticotrophin, it was assumed that this supposed agent would be at greatest concentration in the blood stream of a Na^+-depleted adrenally insufficient sheep.

The *donor* sheep was prepared as follows. The daily D.C.A. supplement was increased from basal of 5 mg./day to 20 mg./day, and the daily Na^+ supplement was withheld. To maintain a Na^+-depleted adrenalectomized sheep in relatively normal condition it is necessary to give four times the basal amount of D.C.A. After three to four days the sheep had become depleted of 400–700 mEq of Na^+ and it was arranged that the last injection of 20 mg. of D.C.A. was given 30–36 hours before the intended cross-circulation experiment. This allowed time for the effect of the D.C.A. injection to wear off and the salivary Na^+/K^+ ratio to return to normal, as it invariably did in an adrenally insufficient animal (Goding and Denton, 1959). The plasma composition of this animal reflected adrenal insufficiency and severe Na^+ depletion.

It was ensured that the sheep with the adrenal transplant was in normal Na^+ balance by giving a large dose of Na^+ 18 and 5 hours before the experiment. Its salivary Na^+/K^+ was normal (20–40), and the plasma composition indicated normal balance. Venous drainage of the blood from the adrenal was arranged, and then the blood from the Na^+-depleted heparinized donor, which stood quietly in its cage, was led from the left carotid artery loop (Fig. 17) to the carotid artery supplying the adrenal transplant of the heparinized sheep in normal Na^+ balance. This loop was completely occluded above and below the transplant by 300 mm. Hg pressure, so that the cross-circulation line was the only source of blood supply. The recipient with a towel over its eyes was gently restrained on its side on a table covered with sponge rubber, about 30–50 cm. below the donor, and it lay quietly for three to five hours without change of cardiac rate. In any case, this animal's adrenal was removed from its circulation once the cross-circulation began, and hence if any disturbance had occurred after this it would have been without effect on the experiment.

The donor blood was reinfused into the carotid artery supplying the parotid so as to provide the maximum sensitivity for response by the biological indicator to any changes of steroid output induced. There are reasons for aiming to replace the cross-circulated blood by the intravenous route, but in order to obtain a significant result it might be necessary to be sure the cross-circulation would continue for at least

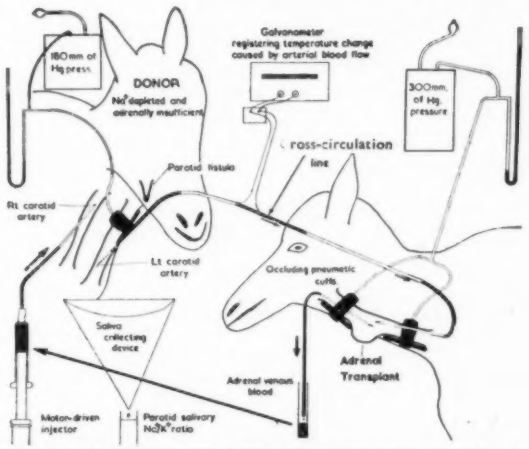

FIG. 17.—Method of cross-circulation in conscious animals. A wide-bore needle and polythene tube inserted into left carotid artery of Na^+-depleted adrenalectomized *donor* leads blood to carotid artery supplying adrenal transplant of *recipient*. This loop is occluded above and below transplant by cuffs at 300 mm. Hg. Adrenal venous effluent is collected from indwelling jugular cannula, and blood is reinfused into right carotid artery loop of donor. Saliva from right parotid fistula of donor is collected and analysed at frequent intervals.

four to six hours. Because a long period of cross-circulation in conscious animals is technically difficult, we have in the first instance preferred this method of short-circuiting the systemic circulation, and have relied upon appropriate control experiments in interpreting the results.

It was found that this cross-circulation caused the parotid salivary Na^+/K^+ ratio to decrease over a maximum range. Fig. 18 shows the result of such an experiment. The intracarotid infusion of 82 ml. of adrenal venous blood of the transplant sheep in normal

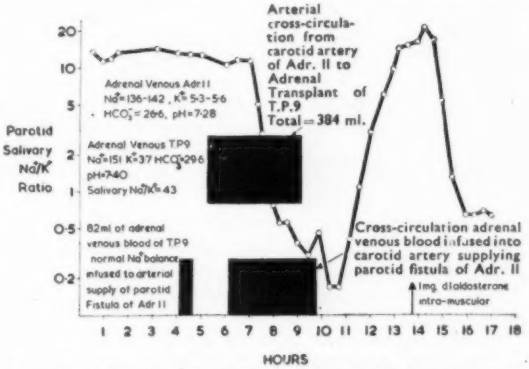
Arterial cross-circulation from carotid artery of Adr. II to Adrenal Transplant of T.P.9 Total = 384 ml.
Adrenal Venous Adr II Na=136-142, K=5·3-5·6 HCO3=26·6, pH=7·28
Adrenal Venous TP9 Na=151 K=3·7 HCO3=29·6 pH=7·40 Salivary Na/K=43
Parotid Salivary Na/K Ratio
20
10
5
2
1
0·5
0·2
82ml of adrenal venous blood of TP9 normal Na balance infused to arterial supply of parotid Fistula of Adr II
Cross-circulation adrenal venous blood infused into carotid artery supplying parotid fistula of Adr. II
1mg. dl-aldosterone intra-muscular
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
HOURS

FIG. 18.—Adr. 11 (bilaterally adrenalectomized and Na^+-depleted). Effect on parotid salivary Na^+/K^+ ratio of (*a*) ipsilateral intracarotid infusion of 82 ml. of adrenal venous blood from T.P.9 (normal Na^+ balance); (*b*) ipsilateral intracarotid infusion of 384 ml. of its own peripheral blood after cross-circulation through adrenal gland of T.P.9; (*c*) intramuscular injection of 1 mg. DL-aldosterone.

Na^+ balance had no effect on the Na^+/K^+ ratio of the adrenally insufficient Na^+-depleted donor sheep. However, after infusion of cross-circulated blood into the carotid artery of the donor sheep there was an early and precipitate fall in salivary Na^+/K^+ ratio. By 120 minutes the ratio had fallen from 194/17=11.4 to 63/114=0.55 (volume of adrenal venous blood infused =212 ml.), and after 264 minutes the ratio was 25/143=0.17. The ratio began to rise sharply 60 minutes after the carotid infusion ceased and was normal 120 minutes later. After it had returned to normal a test dose of 1 mg. of DL-aldosterone was given intramuscularly. About 60 minutes later the ratio fell steeply, but the change (196/12=16.3, to 63/99=0.64) was less than produced by the cross-circulation.

In these experiments three procedures were adopted to ensure that the cross-circulation was running, since, it was possible that, despite the pressure on the occluding cuffs of 300 mm. Hg, the "water-hammer" effect of the pulse would force blood past it if the cross-circulation line clotted. Hence (1) a Wheatstone bridge was constructed in which one arm consisted of a coil of fine wire wound around the cross-transfusion line—this enabled continuous observations to be made on blood flow through the line by virtue of the change in resistance with temperature; (2) the adrenal venous blood was analysed at intervals; and (3) after inflation of the cuffs the plasma of the recipient sheep was marked by intravenous injection of Evans blue, and it was confirmed at intervals that the adrenal blood contained none of this marker.

A second cross-circulation had the same result. It gave greater effect than the standard aldosterone injection.

Control Experiments

The absence of blood-incompatibility problems in these merino sheep carried the advantage that the two cross-circulation animals could be used for many control experiments involving transfer of blood. It was important to show that the procedure of "short-circuiting" the systemic circulation would not itself cause a parotid response. Thus the total adrenal venous blood of T.P.9 in normal Na^+ balance was withdrawn for 195 minutes, at the same rate as the blood flow of a cross-circulation, and infused into the carotid supplying the parotid of the Na^+-depleted, adrenally insufficient sheep. No effect at all occurred during 170 minutes (Fig. 19), whereas in a cross-transfusion a response was fully developed by 120–180 minutes. A response did begin at 170 minutes, but by this time approximately 15% of the circulating blood volume of T.P.9 had been removed via the adrenal vein. It is possible that by this stage this blood loss evoked adrenal-stimulating mechanisms. The standard dose of aldosterone had a larger effect. In a second experiment the total adrenal blood flow was withdrawn for 55 minutes (volume= 486 ml.) and infused without any effect on the salivary Na^+/K^+.

A further condition for control was that in the cross-transfusion there was an abrupt fall of Na^+ concentration and rise of K^+ concentration of the adrenal arterial blood, and hence the above experiment was repeated twice during the course of an infusion of 4% glucose with 10 mEq of KCl/l. added into the adrenal arterial blood. Though Na^+ was reduced by 10 mEq/l. and K^+ increased by 0.5 mEq/l., the effect was very much less than a cross-circulation (Fig. 20). These control experiments showed that the adrenal venous blood of a sheep in normal Na^+ balance had only a small effect on the sensitive biological indicator, whereas the cross-circulation from a Na^+-depleted sheep had an effect similar to that of infusing the adrenal venous blood of a Na^+-depleted sheep (cf. Fig. 7).

A further important control experiment is recorded in Fig. 21. In this instance, the same donor sheep, though adrenally insufficient, was in *normal Na^+ balance*. The cross-circulation caused a decrease of parotid salivary

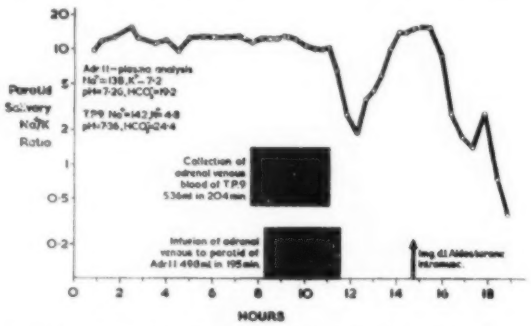

FIG. 19.—Adr. 11 (bilaterally adrenalectomized and Na^+-depleted), 17/4/58. Effect on parotid salivary Na^+/K^+ ratio of (*a*) ipsilateral intracarotid infusion of 498 ml. of adrenal venous blood of T.P.9 (normal Na^+ balance); (*b*) intramuscular injection of 1 mg. DL-aldosterone.

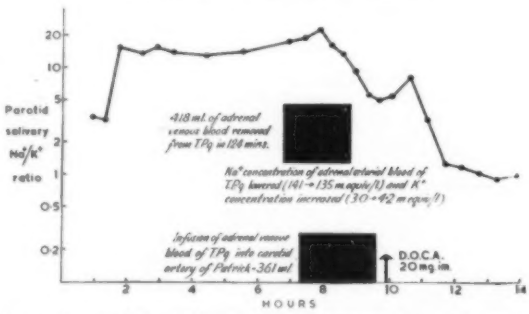

FIG. 20.—Patrick (bilaterally adrenalectomized and Na^+-deficient), 18/9/58. Effect on parotid salivary Na^+/K^+ ratio of (*a*) ipsilateral intracarotid infusion of 361 ml. of adrenal venous blood of T.P.9 (normal Na^+ balance) collected when adrenal arterial Na^+ concentration was lowered and K^+ concentration raised; (*b*) intramuscular injection of 20 mg. D.C.A.

Na^+/K^+, though it was much less than that caused by the standard dose of 1 mg. of DL-aldosterone. A further control procedure is shown in Fig. 21. Since there was variability of the rate of blood flow in the cross-circulation, and it was slower than the normal adrenal blood flow, the adrenal venous blood of T.P.9 was collected for 130 minutes under conditions of much more severe restriction of arterial inflow (rate=1.5–2.5 ml./minute) than occurred in any cross-circulation. There was an effect on adrenal secretion, but the response over the time interval was much less than a cross-circulation relative to the standard 1 mg. of DL-aldosterone injection.

Summary of Results

The results gave indication of a humoral stimulus other than ionic change affecting the adrenal. The principal question is whether or not the humoral agent in the blood stimulating the adrenal in this manner is corticotrophin. Certainly corticotrophin would be at maximal concentration in the blood of a Na^+-depleted adrenalectomized sheep which is the donor in a cross-

circulation. Formally, in considering the role of corticotrophin in adrenal secretion of aldosterone the following possibilities exist: (1) That the anterior pituitary, through corticotrophin, is the normal physiological regulator of adrenal aldosterone secretion, and secretion of corticotrophin occurring in Na^+ depletion stimulates the adrenal. (2) That the adrenal is stimulated to produce aldosterone by either a different humoral agent and/or local adrenal factors, but their action is enhanced by corticotrophin secretion caused by a non-specific stress reaction to the physiological consequence of Na^+ depletion—that is, corticotrophin is a contributory cause of adrenal aldosterone secretion. (3) That corticotrophin secretion, by virtue of ensuring a normal output of glucocorticoids, is a permissive condition of a normal aldosterone secretion (cf. Muller, 1958). (4) That the adrenal secretion of aldosterone is relatively independent of corticotrophin.

The evidence against direct anterior pituitary control of aldosterone secretion is (*a*) the relatively normal electrolyte metabolism in panhypopituitarism and hypophysectomy, and the fact that increased excretion of aldosterone in response to Na^+ depletion may occur in these conditions; (*b*) the failure of large doses of exogenous hydroxycorticosteroids to influence aldosterone secretion in the face of known suppression of anterior pituitary secretion (Ingle, 1938; Sayers and Sayers, 1949; Farrell, Banks, and Koletsky, 1956); (*c*) the much smaller effect of hypophysectomy on the zona glomerulosa, which, on the basis of histological (Deane and Greep, 1946; Deane, Shaw, and Greep, 1948) and isolated slice studies (Ayres, Gould, Simpson, and Tait, 1956; Giroud, Stachenko, and Piletta, 1958), appears to be the site of aldosterone production; (*d*) the relative inconstancy between batches of the effect of corticotrophin on aldosterone secretion and Na^+ metabolism.

In the light of this we made a cross-circulation in which the donor sheep was heavily loaded with hydroxycorticosteroids for 36 hours before the experiment with the object of suppressing endogenous corticotrophin production. The results are shown in Fig. 22. It received 100 mg. of cortisone per day for two days, and on the day preceding the experiment it received 100 mg. of cortisone and 20 mg. of D.C.A. at 3.45 a.m. It was given a further 100 mg. of cortisone at 5.25 p.m. on that day. At 6.55 a.m. on the day of the experiment (nine hours before the cross-circulation) a further 50 mg. of cortisone was given. As can be seen in Fig. 22, this had a small effect on the salivary Na^+/K^+ ratio. Six hours before the transfusion 17 mg. of hydrocortisone (as hemisuccinate) was given by intravenous infusion over a period of five minutes. This caused the ratio to fall again, but it rose over the next two and a half hours despite intravenous hydrocortisone infusion at the rate of 6 mg./hour. Allowing for the weight of the animal (about 30 kg.), this last dose was at least twice that employed by Bethune, Nelson, and Thorn (1957) to suppress corticotrophin production in patients with Addison's disease.

Three hours later the cross-circulation was begun, and this was our most successful experiment technically, in so far as 1.75 litres of blood flowed through the adrenal. The procedure stimulated the adrenal to cause a maximal parotid response, which was sustained for two hours after the infusion of adrenal venous blood was stopped. The donor sheep was then given an infusion of peripheral blood from a sheep in normal Na^+ balance to replace adrenal venous blood taken for analysis. After the parotid salivary Na^+/K^+ returned to normal the usual test dose of 1 mg. of aldosterone was given. The cross-circulation had a much larger effect. *Thus, despite this procedure aiming to suppress corticotrophin secretion, the response was maximal.* The adrenal blood flow increased progressively during the experiment from 4 to 7 ml./minute. This change, concurrent with the development of the response, was further evidence against the response being caused by adrenal haemodynamic effects.

Further suggestive evidence in sheep that corticotrophin was not the primary cause of secretion of aldosterone came from experiments in which Na^+-depleted sheep were given a very large single dose of

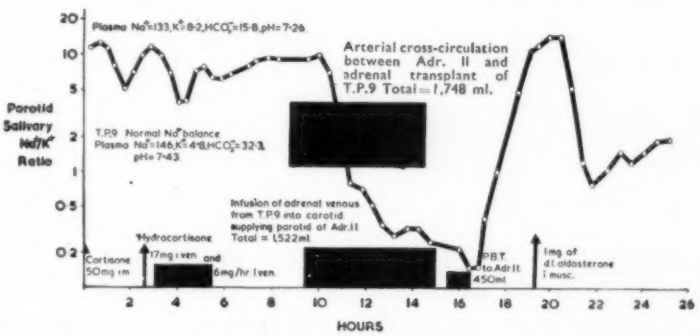
Parotid Salivary Na/K Ratio
Plasma Na+=133, K+=8·2, HCO3−=15·8, pH=7·26
Arterial cross-circulation between Adr. II and adrenal transplant of T.P.9 Total = 1,748 ml.
T.P.9 Normal Na+ balance
Plasma Na+=146, K+=4·9, HCO3−=32·3, pH=7·43
Infusion of adrenal venous from T.P.9 into carotid supplying parotid of Adr.II Total = 1,522 ml
Hydrocortisone
17mg i.ven and
6mg/hr i.ven
Cortisone 50mg i.m.
PBT to Adr.II 450ml
1mg. of dl aldosterone i.musc.
HOURS

FIG. 21.—Adr. II (bilaterally adrenalectomized and in normal Na^+ balance), 7/3/58. Effect on parotid salivary Na^+/K^+ ratio of (*a*) ipsilateral intracarotid infusion of 205 ml. of its own peripheral blood after cross-circulation through adrenal gland of T.P.9 (normal Na^+ balance); (*b*) ipsilateral intracarotid infusion of 216 ml. of adrenal venous blood of T.P.9 collected during severe restriction of blood flow; (*c*) intramuscular injection of 1 mg. DL-aldosterone.

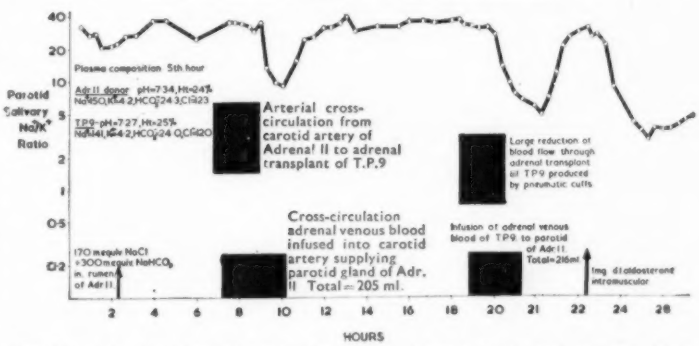
Parotid Salivary Na/K Ratio
Plasma composition 5th hour
Adr.II donor pH=7·34, Ht=24%
Arterial cross-circulation from carotid artery of Adrenal II to adrenal transplant of T.P.9
Large reduction of blood flow through adrenal transplant of T.P.9 produced by pneumatic cuffs
Cross-circulation adrenal venous blood infused into carotid artery supplying parotid gland of Adr. II Total = 205 ml.
Infusion of adrenal venous blood of T.P.9 to parotid of Adr.II Total = 216ml
170 mequiv NaCl + 300 mequiv NaHCO3 in. rumen of Adr.II
1mg. dl aldosterone intramuscular
HOURS

FIG. 22.—Adr. 11 (bilaterally adrenalectomized, Na^+-depleted, and receiving large doses of cortisone and cortisol), 29/5/58. Effect on parotid salivary Na^+/K^+ ratio of (*a*) intramuscular injection of 50 mg. cortisone; (*b*) intravenous injection of 17 mg. hydrocortisone hemisuccinate followed by intravenous infusion at 6 mg./hour of same material; (*c*) ipsilateral intracarotid infusion of 1.52 litres of its own peripheral blood after cross-transfusion through adrenal gland of T.P.9 (normal Na^+ balance); (*d*) intramuscular injection of 1 mg. DL-aldosterone.

cortisone (150 mg. intramuscularly) or hydrocortisone (20 mg. intravenously) followed by an intravenous infusion of hydrocortisone at 13.5 mg./hour for two and a half hours. This dose was again larger than that used by Bethune *et al.* (1957) to suppress corticotrophin secretion, but the salivary Na^+/K^+ remained at its low level during the next seven hours. There was no effect similar to a rapid change of Na^+ balance, a result which might have followed if it were supposed that the adrenal secretion of aldosterone in Na^+ depletion was caused by corticotrophin.

So far, the results of the cross-circulation have shown the stimulus to electrolyte-active secretion to be humoral, and are suggestive of the possibility of a hitherto unrecognized hormone. The results will be convincing in regard to this interpretation if cross-transfusion from a hypophysectomized adrenally insufficient Na^+-depleted donor gives this result. The findings with the biological indicator should at the same time be correlated with chromatographic analysis of the adrenal venous blood.

Other procedures which aim to demonstrate the secretion of a hormone are (1) the loss of the effect after removal of the site of origin, (2) isolation of the substance from excreta, and (3) extraction of the material from the supposed site of origin.

Loss of Effect After Removal of Site of Origin

In considering the loss of the effect after removal of the site of origin, a possibility was that, alternative to the usual view that the adrenal controlled the kidney in certain respects, the kidney might be the site of a receptor sensitive to haemodynamic change or supply of Na^+ and, accordingly, secrete an adrenotrophic hormone. However, this hypothesis fell when a normal parotid response to Na^+ depletion was demonstrated in a nephrectomized sheep. There was, however, positive evidence suggesting that the site might be in the brain. The variation in Na^+-retaining activity between batches of corticotrophin (Selkurt, 1954), and the presence of material stimulating aldosterone synthesis by zona glomerulosa slices in some batches of p.p.e. "infundin" (Giroud *et al.*, 1958), and the stimulation of aldosterone secretion in hypopituitarism by monkey and human growth hormone (Beck, McGarry, Dyrenfurth, and Venning, 1957), raises the question of the presence of a contaminant in some preparations. Inspection of the bulk material used for extraction by the laboratory producing corticotrophin here in Australia showed that the material sometimes included a considerable amount of pituitary stalk with the hypothalamus often adherent.

There have been reports of salt-wasting syndrome in patients with some cerebral diseases (Peters, Welt, Sims, Orloff, and Needham, 1950; Welt, Seldin, Nelson, German, and Peters, 1952). Rauschkolb and Farrell (1956) have reported that, in dogs, decerebration or decapitation reduces the aldosterone content of adrenal venous blood collected during anaesthesia to 25%, whereas hypophysectomy reduced it to only 66% of the control group (Rauschkolb, Farrell, and Koletsky, 1956). These dogs, which were anaesthetized with pentobarbitone sodium, were presumably in normal Na^+ balance, and the procedure involved the collection of a considerable fraction of the animal's blood volume via the adrenal vein. In a study on the secretion of the acutely transplanted adrenal (Fleming and Farrell, 1956), reference was made to the replacement of this blood by infusion of dog blood. However, in other studies (Rauschkolb *et al.*, 1956; Farrell *et al.*, 1956; Rauschkolb and Farrell, 1956; Farrell, Fleming, Rauschkolb, Yatsu, McCally, and Anderson, 1958) this does not appear to have been done. Hence the baseline conditions relative to which a putative agent was examined were the combined effects of trauma, anaesthesia, and blood loss.

The rates of secretion of aldosterone for the control groups in these experiments—20–30 μg./100 kg. body weight/hour—are of the order reported by Reich and McDonald (1958) for Na^+ deficiency in the conscious sheep. The result is clearly seen in the experiments on the effect of blood loss (Farrell, Rosnagle, and Rauschkolb). There were six groups, each of five to seven dogs, and consecutive adrenal venous collections were made at 20-minute intervals for 180 minutes. For the pooled specimen during the first 20 minutes, the mean aldosterone detection rates of the groups were 8.8, 23.2, 9.3, 15.1, 8.5, and 9.5 μg./100 kg. body weight/hour. The reason for the variation between groups was not immediately evident. The secretion rate doubled or more during the 180 minutes of collection of adrenal blood. The aldosterone detection rates during the first 20 minutes corresponded in some groups to the reduction from control values caused by decerebration (Rauschkolb and Farrell, 1956). Thus decerebration appeared to reduce the adrenal stimulus resulting from severe blood loss. It remains to be determined whether comparable removal of the nervous system dislocates the adrenal stimulation resulting from Na^+ deprivation. The possibility of variability of assay under conditions of this complexity was shown in the investigation of steroidogenic properties of purified corticotrophins (Farrell *et al.*, 1958), where a considerable difference was found between the effect of two specimens of corticotrophin from the same original lot.

The question arises whether, from a quantitative aspect as well as from the viewpoint of the supposed mechanism to be demonstrated, the decerebration evidence might be advanced by including observations on Na^+-deficient animals—that is, on those already secreting aldosterone at a convincing rate in response to the normal stimulus. Investigations in this laboratory have examined (*a*) whether removal of the brain rostral to the pons in a Na^+-deficient animal causes changes similar to rapid correction of Na^+ deficiency; (*b*) whether removal of the brain rostral to the pons interfered with the changes following rapid correction of Na^+ deficiency; and (*c*) whether the same extent of brain removal in a Na^+-replete animal alters the response to Na^+ deficiency.

The investigation is still in progress, and at this stage we can only report (*a*) that such decerebration does not reproduce the whole effect of rapid correction of Na^+ deficiency, though in some instances the salivary Na^+/K^+ did rise 120 minutes after the operation by one-third of the amount necessary to return it to normal; (*b*) a normal response occurred after rapid correction of Na^+ deficiency made eight hours after a considerably more rostral decerebration—that is, quadrigemina and portion of mammillary bodies intact; and (*c*) 36 hours after decerebration and hypophysectomy were carried out on a Na^+-replete animal it was depleted of about 500 mEq of Na^+ (bilateral parotid secretion and buccal saliva loss). The salivary Na^+/K^+ ratio had fallen from 11–12 to 3–4.

In these experiments the surgical procedures of vessel ligation preceding decerebration usually lowered the

salivary Na^+/K^+ ratio, as did the operation of decerebration itself in a Na^+-replete animal. Thus factors unrelated to change of Na^+ balance were acting, at least temporarily, under the conditions of these experiments, and this will have to be taken into account in any eventual attempt to interpret results.

Isolation of Substance from Excreta

Orti, Ralli, Laken, and Dumm (1957) reported that extracts of urine of Na^+-depleted adrenalectomized rats when injected into normal rats caused Na^+ retention. The effect, however, was not large. Dr. R. Bradley and Mr. J. Nelson used the same procedure to make an extract of 16 hours' output of urine in the Na^+-depleted adrenally insufficient sheep used in the cross-circulation. Infusion of this extract during 368 minutes direct into the adrenal arterial supply of a mildly Na^+-depleted sheep had no effect on the salivary Na^+/K^+ ratio.

Extraction of Material from Supposed Site of Origin

Farrell (1957) has reported preparing a diencephalic extract which stimulated aldosterone output in adrenal venous blood of decerebrate dogs. In collaboration with Dr. Bradley and Mr. Nelson we have taken the heads off 450 sheep within three minutes of death, and removed the ventral hypothalamus and pituitary stalk. The pieces were collected into a beaker at $-60°$ C. The anterior pituitary was not included. So far it has been found that intravenous injection of a saline extract of the residue after acid-acetone extraction of the material has reduced or prevented the normal response to rapid correction of Na^+ deficiency (Fig. 23). The

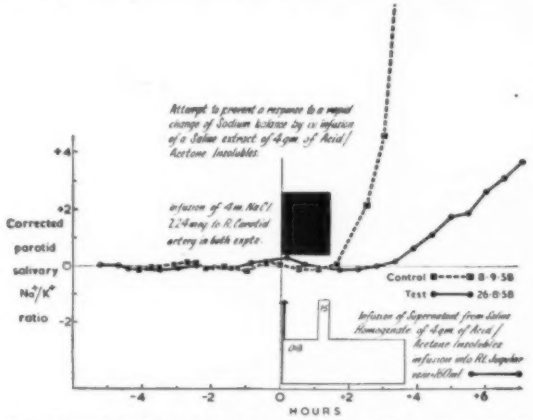
Attempt to prevent a response to a rapid change of Sodium balance by iv infusion of a Saline extract of 4 gm. of Acid/Acetone Insolubles.
infusion of 4 m. NaCl 2.4 meq. to R. Carotid artery in both expts.
Corrected parotid salivary Na+/K+ ratio
+4
+2
-2
Control 8-9-58
Test 26-8-58
Infusion of Supernatant from Saline Homogenate of 4 gm of Acid/Acetone Insolubles infusion into Rt Angular vein+Blood
-4
-2
0
+2
+4
+6
HOURS

FIG. 23.—Ned (Na^+-depleted), 26/8/58. Effect on parotid salivary response to rapid correction of Na^+ deficiency of intravenous infusion of the supernatant of a saline homogenate of ventral hypothalamus (see text): ●——●. Control experiment: ■- - - -■.

effect has not yet been tested by infusion in hypophysectomized animals or at one-thousandth of this concentration direct into the adrenal circulation, nor have any experiments been made to determine to what extent the effect might be attributable to extraction of an area particularly rich in pharmacologically active materials. The assertion by Stack-Dunne and Young (1954) in relation to corticotrophin that chemical artifacts with biological activity can be produced by extraction procedure would be a further reason for not supposing at this stage that this effect is related to any agent which circulates in the blood under physiological conditions.

Nature of Stimulus to Receptor Controlling Aldosterone Secretion

If there is a hormonal factor contributing to regulation of aldosterone secretion the question arises of the stimulus to its release. The receptor may not be in the same place as the tissue secreting the humoral agent, and we have alluded already to the possibility that the effective stimulus or stimuli may be other than the ionic concentration changes shown to be active at the adrenal level. Two initial possibilities to be considered are whether the mechanism (*a*) is akin to a Na^+-accounting machine in that, for example, serially arranged transfer mechanisms in a specific local vascular field register the load of Na^+/unit time in the local blood supply; or (*b*) is responsive to some physiological consequence of change in the amount of fluid in the vascular or extracellular compartment of the body—for example, stimulation of a pressure or stretch receptor, or determining the area of surface available for a particular transfer process.

It has been shown in the sheep that there is a normal response to Na^+ depletion when concurrent water depletion caused a rise of plasma Na^+ during Na^+ deficiency instead of the usual fall (Denton, 1958). Furthermore, there is a normal response if Na^+ deficiency is corrected rapidly by the infusion of hypotonic NaCl (2 l. of 102 mEq/l. during 40 minutes) so that no rise of plasma Na^+ occurs. Gross water deficiency, which causes a considerable contraction of plasma volume, does not cause a decrease of salivary Na^+/K^+ ratio. If the sheep which is concurrently depleted of water and Na^+ for several days is allowed to drink 3–4 litres of water there is a rapid fall of plasma Na^+, and other evidence of expansion of plasma volume, but no effect on the salivary Na^+/K^+ ratio (Denton, 1958). These experiments do not, however, effectively decide between the alternatives. We prefer to defer discussion of these and other experiments involving alteration of compartment volumes and pressure of circulating fluids, and deal here with another general biological aspect of the problem.

In considering the stimulus to a putative diencephalic system controlling aldosterone, it would seem prudent to bear in mind at the outset the known complexity of other forms of chemical regulation. The control of respiration is a case in point where changes in the milieu with regard to pCO_2, *p*H, and pO_2 may have additive or antagonistic effects on respiration, and other afferent influences via the vagus, from the cortex, or from other centres, such as preoptic thermoreceptors, may be determinant (Pitts, 1946; Gray, 1950; Andersson and Persson, 1957). Similarly, the work of ethologists—for example, Lorenz (1950), Tinbergen (1951), and Thorpe (1958)—has shown that some of the hierarchically organized neural mechanisms influencing hormonal secretion in the course of determining behaviour are very complex indeed. In this vein, and consistent with the inquiry described by Richter (1958), we wish to describe the remarkable appetite for salt shown by Na^+-deficient animals.

A Na^+-depleted sheep will lick much more from a block of rock salt than a sheep in normal Na^+ balance (Denton, 1957a). When sheep with parotid fistulae were offered a choice of solutions—for example, 420 mEq of NaCl/l., 420 mEq of $NaHCO_3$/l., 140 mEq of KCl/l., and H_2O—it was found that they drank much more of the Na^+-containing solutions when the daily supplement of

$NaHCO_3$ was withdrawn (McDonald and Raschke, unpublished). Moreover, some animals first drank NaCl, but after six to eight days they drank predominantly $NaHCO_3$—a more appropriate choice in the face of the loss of $NaHCO_3$ from the parotid fistula. With subsequent episodes of Na^+ deficiency they showed a preference for $NaHCO_3$ at the outset.

Further studies (Sabine and Denton, unpublished) have shown that intake is related to need. If $NaHCO_3$ solution and water were available to the animal, and the concentration of the $NaHCO_3$ solution was varied, the volume drunk varied inversely with the concentration (Fig. 24). Thus the average daily intake for the period remained nearly constant and was remarkably close to the Na^+ loss from the fistula. If the Na^+-containing solutions were made available for only 15–60 minutes each day, the animals nevertheless drank adequate Na^+ to maintain balance. When a sheep was

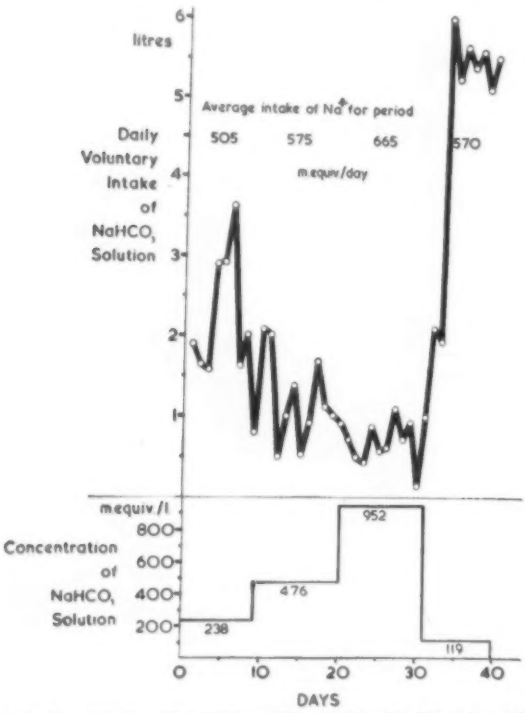

FIG. 24.—P.F.33, May/June, 1957. Intake in litres/day of $NaHCO_3$ solution, concentration of which was changed every 10–11 days. Animal had access to $NaHCO_3$ solution and H_2O during whole day. Daily loss from its fistula was 3–4.5 litres (from Sabine and Denton, unpublished).

in normal Na^+ balance it paid little attention to the usual observer preparing the Na^+ solutions and placing them in position. However, an animal with experience of the procedure would, when Na^+-depleted, bleat and kick the side of its cage, and there was a large psychic secretion of saliva (cf. Denton, 1957c) when it saw the preparatory moves. The finding that the animals would take adequate Na^+ when only a short period of access was permitted opened the way for detailed analysis of the behaviour entailed in the satisfaction of the Na^+ appetite.

Observation of the sampling behaviour showed that when the animal was given access to the series of solutions, NaCl, $NaHCO_3$, KCl, and H_2O, the number of sampling episodes/hour—for example, smelling, tasting, or drinking—increased greatly during Na^+ deficiency (Fig. 25). The evidence on rejection or acceptance of a solution, according as they were

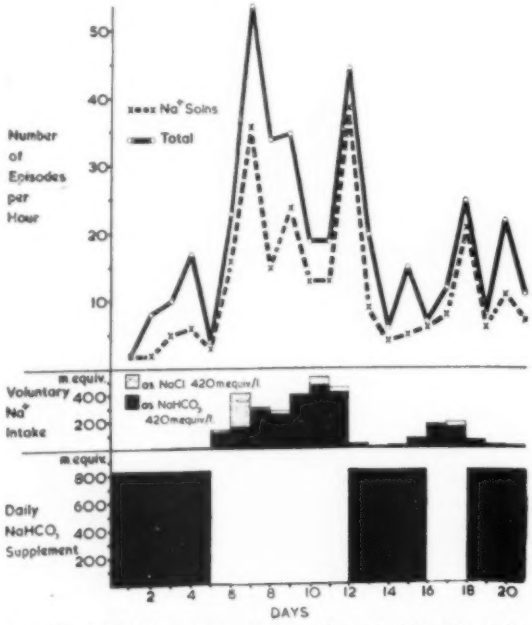

FIG. 25.—P.F.33, Aug./Sept., 1957. Effect of withholding daily supplement of 800 mEq $NaHCO_3$ on voluntary intake of solutions of $NaHCO_3$ (420 mEq/l. and NaCl (420 mEq/l. which were available for one hour/day only. Number of episodes of sampling (smelling, tasting, drinking) all solutions ($NaHCO_3$, NaCl, KCl, and H_2O) O——O, and number of episodes involving Na^+ solutions × - - - - × are shown in upper section (from Sabine and Denton, unpublished).

encountered in the initial survey by the animal, also corresponded to the preference shown in the overall intake. Preliminary experiments have been made in which one carotid artery loop was occluded and an infusion of 4 M NaCl made into the other at 1.6 ml./minute. This raised the Na^+ concentration of the blood on both sides of the head by 20 mEq/l. during the 15-minute period of choice, but the infusion itself repaired the animal's Na^+ deficiency by a small degree only. During normal Na^+ balance this caused the sheep to drink water. In Na^+ deficiency this did not happen, but the procedure significantly reduced the animal's intake of Na^+. Moreover, following a number of such episodes on alternative days of depletion, the animal was permitted access to the solution without an infusion. There was residual modification of behaviour in that Na^+ intake was still reduced despite deficiency, though there was great interest in the Na^+ solutions as evidenced by greater than usual frequency of tasting. Subsequent to a period of normal Na^+ balance without testing, the animal manifested its usual ability to drink a large and adequate amount of Na^+ solution when deficient.

Sheep have been concurrently depleted of both Na^+ and water so that there was a rise of plasma Na^+ concentration during deficiency instead of the usual fall, and the behaviour was compared with that seen in the same animal during either uncomplicated water deficiency or Na^+ deficiency. When offered water and

Na^+ solution the animal's brain appeared quite able to differentiate the situations. With uncomplicated depletions the animal rejected one solution but avidly drank the appropriate one. With the concurrent depletion it would accept either initially. Having drunk a large amount of one it would refuse more but immediately drink a large amount of the other if offered. If both were offered simultaneously the animal would satisfy itself with one and immediately pass to the other and drink it. In these studies, measurements of plasma volume were made as well as comprehensive plasma analyses, and it is interesting to note that in one group the plasma volume was reduced a comparable amount by each type of depletion. The type of fluid drunk, however, was specifically related to the deficiency. On the other hand, in many studies of the series, there was little evidence of relation between readiness to drink Na^+ solutions and the concentration of Na^+ in the plasma.

Central Integration of Individual Systems Regulating Na^+ Balance

This brief account may serve to indicate that because of the magnitude of the electrolyte losses, and because the size of the animal permits staged surgical procedures and complicated manipulations, there is a promising field for investigating the mechanism of appetite. The question arises whether the provoking stimuli are the same as those determining aldosterone secretion in the animal. It is possible that, just as the function of other diencephalic and brain-stem regulatory centres may determine or be determined by cerebral cortical events, so may this remarkable selective appetite for Na^+ be the cerebral behaviour determining projection of a Na^+ regulatory centre which also influences a hormonic stimulus to aldosterone secretion. We have referred already to the finding that the normal inhibition of adrenal secretion following rapid correction of a Na^+ deficiency may be prevented or modified if the significance of distance receptor information induces a state of apprehension in the animal. Further, Andersson, Jewell, and Larsson (1958) have shown that stimulation in the hypothalamus between the fornix and mammilo-thalamic tracts, but lateral to the drinking area, induces vigorous licking of a salt block in the goat.

There is a parallelism between this group of findings and the established facts on antidiuretic hormone secretion, osmoregulation, thirst, the inhibition of an established water diuresis by fear or disturbance (Verney, 1947), and the demonstration of compulsive drinking upon localized hypothalamic stimulation. If a neural-organization-regulating Na^+ does exist, it appears to be separate from the osmoregulating system in that intracarotid injection of 2.7M glucose, an adequate osmotic stimulus, does not appear to affect it, and the selective appetite during concurrent water and Na^+ deprivation shows that the animal's brain readily distinguishes the two situations. The evocative stimulus of such a Na^+-regulating neural centre may be, as with osmoregulation, predominantly the result of change of a single property of the *milieu intérieur*, or it may be that, analogous to respiratory control, a number of factors may be effective, and the eventual demonstration that one factor is effective need not rule out the efficacy of other stimuli any more than the demonstrable response of the respiratory mechanism to pCO_2 excludes the fact of its response to pO_2, *p*H, and many other influences.

Similarly, the quantitative effect of a trophic hormone at the adrenal level might be the resultant of an interplay of many factors including the direct effect of ionic changes in adrenal blood as well as, for example, the effect of corticotrophin in a permissive or contributory causal role. Of course, it may be that the two systems contributing to Na^+ regulation—namely, aldosterone secretion and selective appetite for Na^+—are only loosely functionally linked if at all, and the evoking stimuli to the two systems may be different. However, the complex integration of behaviour-determining mechanisms with hormonal components in simpler species—for example, the three-spined stickleback—could encourage the view that integration of comparable complexity could be involved in the evolution of a mechanism as important for survival of higher species as sodium control. A unifying hypothesis of a brain centre is provocative of useful experiments aiming to elucidate the issue, and has the coincident virtue of encouraging consideration of the clinical investigation of aldosterone regulation in the general biological context.

Summary

The paper describes experiments aiming to solve the clinically important question of how the adrenal secretion of aldosterone is controlled. To investigate the control of secretion of a hormone it is desirable that the experiments be made on conscious confident animals and it be contrived that there is easy access to the arterial supply and venous drainage of the endocrine gland under these conditions. The neck adrenal transplant preparation permits, in conscious sheep, experiments aiming to determine whether the gland responds directly to changes of arterial sodium and potassium concentration or whether it responds to a hormonal stimulus.

The results indicate that changes of adrenal ionic environment may be a contributory cause of changes of electrolyte-active steroid secretion occurring in sodium deficiency, but they do not account for the whole range of function which the gland shows.

Cross-circulation experiments in conscious animals have shown that there is a large stimulation of adrenal secretion of electrolyte-active steroid when the blood of a sodium-depleted adrenally insufficient donor animal is passed through the adrenal transplant of another in normal sodium balance. As this stimulation does not appear to be due to corticotrophin, further experiments have been based on a working hypothesis that a hitherto unrecognized hormonic stimulus originates in the neuraxis. With such a working hypothesis, a fact for concurrent consideration is the remarkably accurate appetite for sodium solutions shown by sodium-deficient sheep.

A possible view of the evidence discussed is that the evolution of control of such an important regulation as sodium balance involves central integration of a number of mechanisms, and that the selective appetite for sodium and the stimulation of aldosterone secretion are functionally linked together.

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deoxycortone acetate used in this work during the past four years, and Boots Pure Drug Co. for donations of cortisone and heparin. We are much indebted to the members of our Unit—Messrs. J. Coghlan, B.Sc., J. Blair-West, B. Dyzenhaus, J. Sabine, B.Ag.Sci., and P. Gardner for their enthusiastic participation, including overnight and week-end procedures, and to Miss Carmel Harrison for her help with experimental records and preparation of papers.

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RESPONSES OF 6- AND 9-MONTHS-OLD INFANTS TO TWO AND THREE DOSES OF POLIOMYELITIS VACCINE

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The earliest time to start immunization against poliomyelitis is when satisfactory response will follow in all subjects. We have already shown that the response to active immunization in infants with high levels of maternally transmitted antibody is unsatisfactory (Perkins, Yetts, and Gaisford, 1958, 1959a). It was not possible to overcome the inhibitory effect of these antibodies in 1-week-old infants with current vaccines, even though the volume and number of the antigenic stimuli are increased, but we were able to show that in 16-weeks-old infants a more satisfactory basal immunity followed primary immunization with three doses of vaccine given at monthly intervals, though the maternal antibody still present in some of these infants inhibited their response to the most important component, type 1 (Perkins, Yetts, and Gaisford, 1959b). It seems clear, therefore, that satisfactory response will not be obtained in all infants until maternal antibody has fallen to non-inhibitory levels, and it is estimated that this will not be until after the age of 6 months.

An investigation was therefore made of the responses of 6- and 9-months-old infants both to two and to three doses of vaccine given as a primary course of immunization.

Procedures

Immunization of Infants.—Thirty-two infants were given intramuscularly three doses of vaccine, each of 1 ml., at intervals of four weeks. Post-immunization

blood samples were taken (*a*) four weeks after the second dose, which was at the time of the third dose, and (*b*) 14 to 21 days later. The infants were in two groups; 16 were 6 months old and 16 were 9 months old at the time of their first injection.

Vaccine.—Two batches of commercial vaccine were used and each group of infants was inoculated with a single batch. The 6-months-old infants were inoculated with vaccine A, prepared from Brunenders (type 1), MEF-1 (type 2), and Saukett (type 3), and that used for the 9-months-old infants—vaccine B—had the type 1 component prepared from the Mahoney strain. The antigenic activity in monkeys showed both vaccines to be satisfactory, with the type 1 potency of vaccine A being a little better than that of vaccine B.

Titration of Sera.—Sera were titrated by the method used in previous investigations (Biological Standards Control Laboratory, 1957; Perkins, Sousa, and Tobin, 1958). For each infant all serum samples were titrated in parallel in the same test in order that a valid comparison of antibody levels could be made. All titres are given as the dilution of serum in the serum–virus mixtures before the addition to cell cultures.

Antibody Levels Before Immunization

Table I gives the distribution of antibodies before immunization in all infants. Three infants had very high levels, two to type 1 and one to type 3. For this reason, and also because these infants gave exceptionally high antibody responses to the first two doses of vaccine, it was considered that they had been infected with poliomyelitis virus during the first few months of life. They were therefore eliminated from further analysis; this left 15 infants in the 6-months-old and 14 in the 9-months-old groups. As might be expected, there was a higher proportion of infants with maternal antibody in the 6-months-old group than in the 9-months-old group. However, maternal antibody had fallen to non-inhibitory levels (<64) to all types in all the 9-months-old infants and in all but two of the 6-months-old infants.

Response to Vaccine

The proportion of infants responding to two and three doses of vaccine and the geometric mean titre for each group are shown in Table II; the levels of responses are shown in the figure.

After two doses the responses to type 2 and 3 were good. There were only two infants, both in the 6-months-old group, who did not respond—one to type 2 and one to type 3—and both had inhibitory maternal antibody levels at the time of receiving the first dose of vaccine. The responses to type 1 were not so good; though they were better in 6-months-old than in 9-months-old infants. Three 6-months-old and six 9-months-old infants failed to respond and the 6-months-old responders gave slightly higher levels than those from the 9-months-old group.

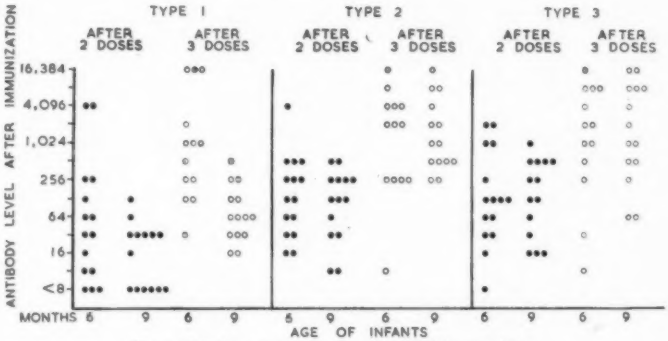

Chart showing responses to poliomyelitis vaccine.

After three doses the responses were entirely satisfactory. All except the two infants who had inhibitory maternal antibody levels responded to all types, and the geometric mean titres for the groups increased by about tenfold. In comparing these results with those obtained in previous studies it is evident that better responses were obtained in these infants to the three-dose schedule than after injection of two doses of vaccine at any other age (Medical Research Council, 1957, 1958).

It is interesting to note that there was very little difference between the 6- and 9-months-old groups in

TABLE I.—*Placentally Transmitted Maternal Antibody Levels to Poliomyelitis Virus Remaining in 6- and 9-months-old Infants*

Age of Infants	No. of Subjects	Virus Type	No. of Sera with Antibody Level											
			<8	8	16	32	64	128	256	512	1,024	2,048	4,096	8,192
6 months	16	1	11	1	0	1	2	0	0	0	0	1	0	0
		2	8	1	4	1	0	2	0	0	0	0	0	0
		3	11	1	1	1	1	2	0	0	0	0	0	0
9 ,,	16	1	13	1	1	0	0	0	0	0	0	0	1	0
		2	13	0	1	0	2	0	0	0	0	0	0	0
		3	13	1	1	0	0	0	0	0	0	0	0	1

TABLE II.—*Proportion of 6- and 9-months-old Infants Responding to Two and Three Doses of Poliomyelitis Vaccine*

Age of Infants	Vaccine	Proportion of Infants Responding (and Geometric Mean Titre)					
		Type 1 After		Type 2 After		Type 3 After	
		2 Doses	3 Doses	2 Doses	3 Doses	2 Doses	3 Doses
6 months ..	A	12/15 (39)	13/13 (870)	14/15 (140)	12/13 (1,080)	13/15 (122)	12/13 (1,140)
9 ,, ..	B	8/14 (8)	14/14 (71)	14/14 (100)	14/14 (1,378)	14/14 (134)	14/14 (1,520)
All infants ..		20/29 (18)	27/27 (237)	28/29 (119)	26/27 (1,226)	27/29 (128)	26/27 (1,322)

their responses to types 2 and 3, after either two or three doses of vaccine. The difference in the type 1 responses after two doses, however, was much accentuated by giving a third dose. Though all infants in both groups responded, the geometric mean titre for the 6-months-old group was more than twelve times that of the 9-months-old group. These results suggest that the antigenic activity of the type 1 component of vaccine A which was given to the 6-months-old infants was greater than that of vaccine B given to the 9-months-old infants.

Conclusions

Placentally transmitted maternal antibody had fallen to non-inhibitory levels in almost all 6-months-old infants and in all 9-months-old infants tested.

The responses of infants in these age groups to two doses of vaccine were good to the type 2 and 3 components, all infants responding, but those to type 1 were not quite so satisfactory because 3 out of 15 6-months-old and 6 out of 14 9-months-old infants failed to show a rise in antibody level. The responses after three doses, however, were much more satisfactory, all infants responding to type 1 giving higher antibody levels, and the responses to types 2 and 3 being very much higher than after two doses.

The 6-months-old infants responded better to type 1 than the 9-months-old infants, and this difference was most pronounced after the third dose. This was probably due to the difference in the antigenic activity of type 1 in the two vaccines used. Though a small difference was observed when measured in monkeys, it was not as marked as in the infants. It is important, therefore, that only vaccines highly potent in the type 1 component should be used for immunizing infants, and that three doses given at monthly intervals should constitute the primary course at this age.

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Since 1955 the medical and health services in Mauritius have been considerably expanded under a plan for capital expenditure. Part of the service was concerned with an island-wide campaign to eliminate malaria, which was previously regarded as a scourge of the colony. The effectiveness of the campaign can be gauged by a comparison of cases within a period of the last 12 years: in 1945 more than 3,000 cases of malaria were treated in hospitals, with a total of 148 deaths; in 1957 only four cases were treated in hospitals, with no deaths reported.

TESTS FOR PHENYLKETONURIA

RESULTS OF A ONE-YEAR PROGRAMME FOR ITS DETECTION IN INFANCY AND AMONG MENTAL DEFECTIVES

BY

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The diagnosis of phenylketonuria is important for three different reasons: in young infants the detection of this metabolic error permits treatment with a low-phenylalanine diet in order to prevent or minimize mental deterioration; the ascertainment of all cases of phenylketonuria among mental defectives would permit an accurate estimate of the frequency in the population of the gene responsible; to the paediatrician the differentiation of phenylketonuria from other forms of mental deficiency is always important, not least because of the light it throws on the chances of later children in the family being affected. For these reasons any test which makes the diagnosis of phenylketonuria simpler or more reliable is to be welcomed.

Several workers have reported that phenylketonurics treated with a low-phenylalanine diet from the age of a few weeks developed normal intelligence, while in cases where treatment was delayed the I.Q. usually remained below the average, and in untreated phenylketonurics the modal I.Q. was 10 (Horner and Streamer, 1956, 1959; Armstrong, Low, and Bosma, 1957; Woolf, Griffiths, Moncrieff, Coates, and Dillistone, 1958; Hsia, Knox, Quinn, and Paine, 1958; Brimblecombe, Stoneman, and Maliphant, 1959; Armstrong, Centerwall, Horner, Low, and Weil, 1959). This emphasizes the importance of early detection if irreversible mental deterioration is to be avoided. Programmes aimed at detecting all cases in a community at a very early age have been suggested or initiated (Woolf, Griffiths, and Moncrieff, 1955; Centerwall, 1957a, 1957b; Hsia, 1957; Woolf *et al.*, 1958; Baird, 1958). We report here the findings of such a detection programme carried out in Cardiff over the period March 1, 1958, to March 1, 1959, and also a survey of four institutions for mental defectives. "Phenistix," a strip which is dipped into the urine like litmus paper, has been found to be a simple and satisfactory test for phenylketonuria.

Method

The mother of every child born in Cardiff was asked to bring a fresh specimen of her baby's urine to the infant-welfare clinic when the baby was 3 weeks old or as soon as possible after. A bottle containing a little chlorbutol as a preservative was provided by the health visitor. Ferric chloride solution (5%) was added drop by drop to the urine until a definite colour appeared.

Results

Though there were 4,530 live births in Cardiff during the year, only 1,192 specimens of urine were collected and tested. The mothers of the 73.7% of babies that were not tested generally complained that it was

impossible to get a specimen of urine, the baby passing urine only when wearing a napkin.

Of the specimens tested, 51 were strongly alkaline, and were rejected. Out of the remaining 1,141 specimens, one gave a positive reaction for phenylpyruvic acid. The infant was admitted to Llandough Hospital under Professor A. G. Watkins, and phenylketonuria was confirmed by chromatography of the serum for phenylalanine. Treatment on a low-phenylalanine diet was started at the age of 1 month. On her first birthday this child had a G.Q. of 94 (Griffiths scale), and her weight was 24 lb. 13 oz. (11.25 kg.).

Seven other infants passed urine that gave a green colour with ferric chloride, exactly like that given by phenylpyruvic acid. However, laboratory investigations by Mr. R. A. Saunders showed that the condition was not phenylketonuria. The positive reactions were found to be due to *p*-hydroxyphenylpyruvic acid. These findings will be described in greater detail elsewhere.

Since December, 1958, infants' urines that were being tested with ferric chloride have also been tested with phenistix. The phenistix method was found to be so much simpler and the results so concordant (except when the urine contained *p*-hydroxyphenylpyruvic acid, see below) that it is proposed to extend the use of phenistix to the infant-welfare clinics when a supply is available, and, perhaps, later to issue the strips to health visitors for use in the home.

Mental-deficiency Survey

In addition to the detection programme for infants, all the children attending a junior school for educationally subnormal children and two centres for mentally defective children, as well as children in a local institution for mental defectives, had their urines examined, using the ferric chloride test. Out of 279 children, two cases of phenylketonuria were found. One of these was a 7-year-old boy who is now being treated on a diet low in phenylalanine; he is much easier to manage than before treatment. The other case detected was that of a 13-year-old who was regarded as untreatable.

Phenistix strips have also been used for examining a urine specimen from one of these children. The reagent strips were found far more convenient to use than the ferric chloride solution, and the results were in complete agreement.

Discussion

Detection of phenylketonuria must be made as early as possible if the affected infant is to have a reasonable chance of growing up mentally normal. These infants do not excrete phenylpyruvic acid at birth, and the best age for testing for it is not easy to determine: the first appearance of phenylpyruvic acid in the urine has been reported at ages ranging from 6 days to 6 weeks. About half the children in Great Britain are born in a hospital or nursing-home, where the organization of tests would be easy, but the infants leave after 10 days, when a large proportion of phenylketonurics do not yet excrete phenylpyruvic acid; there is a serious risk that the child would not be retested if it were known that his urine had already been examined, and this risk becomes greater as the difficulty of testing increases. Three weeks has been suggested as a compromise age for testing the urine—an age when the great majority of phenylketonurics will be excreting phenylpyruvic acid, but mental deterioration will still be slight (Woolf *et al.*, 1958). Retesting at about two months is recommended. Armstrong *et al.* (1959) have reported on six phenylketonurics observed from earliest infancy; some excreted large amounts of phenylpyruvic acid by the seventh day of life, while one did not excrete this acid until 5 weeks old. They suggest that if the urine were tested at the age of 2 weeks most cases would be detected.

The difficulty in obtaining a specimen of urine was by far the greatest single factor limiting the use of the test. Of the children born in Cardiff during the year, only a quarter had their urine tested. If a wet napkin could be tested for phenylpyruvic acid, nearly every child could be tested by the health visitor either at home or at the infant-welfare centre. Phenistix strips seem, at the moment, the best way of using a wet napkin, but there is room for improvement, particularly when the napkin is merely moist.

Where an appreciable volume of urine is available there is a choice of tests. Ferric chloride solution is the most widely used reagent; it should be used without mineral acid. The addition of quite a small amount of sulphuric or hydrochloric acid can invalidate the ferric chloride reaction by depressing the *p*H below that at which any appreciable colour is produced (Woolf, in preparation; cf. Følling and Sydnes, 1958).

p-Hydroxyphenylpyruvic acid occurs in the urine of infants fed large doses of tyrosine or phenylalanine (Levine, Marples, and Gordon, 1939, 1941; Levine, Dann, and Marples, 1943; Woolf and Edmunds, 1950), of sufferers from scurvy (Rogers and Gardner, 1949; Morris, Harpur, and Goldbloom, 1950), of adults and children with hepatic cirrhosis (Felix, Leonhardi, and Glasenapp, 1951; Woolf, unpublished), and, as briefly reported above, of a number of normal infants (Gibbs and Woolf, in preparation). It is difficult to distinguish *p*-hydroxyphenylpyruvic acid from phenylpyruvic acid by using ferric chloride or 2:4-dinitrophenylhydrazine; the two acids can be differentiated by using phenistix and observing the colour on the strip, but not if the reagents on the strip are leached out into the urine. The use of Briggs's reagent (cf. Woolf and Edmunds, 1950; Berry and Woolf, 1952) allows these two acids to be distinguished.

A positive reaction by any test must not be taken as conclusive proof of the diagnosis unless supported by, for example, serum phenylalanine determination. In the case of a "high-risk" group, such as the sibs of known cases of phenylketonuria, it is in any case advisable to carry out this laborious procedure at the ages of, say, 1, 2, 3, and 6 weeks, as well as using one of the simple urine tests as often as possible. Armstrong *et al.* (1959) suggest the determination of serum phenylalanine after one or two days of life in such cases.

The results of a detection programme in infants such as that reported here are of little use for determining the frequency of the gene in the population, because the high "failure rate"—75%—in this case is almost certainly not random. The great majority of phenylketonurics are eventually placed in institutions, and by determining the number of phenylketonurics in mental-deficiency institutions in an area the incidence in the population can be ascertained with fair accuracy. A large number of urine specimens have to be tested, and the test used should be as simple and speedy as possible. Dipping a

phenistix strip into the specimen is the quickest test available, and requires least in the way of apparatus, chemicals, or special skills.

Summary

A programme aimed at testing for phenylketonuria the urine of all infants born in Cardiff achieved only a 25% success. None the less, one case was detected and treated successfully. It is difficult to get a suitable specimen of urine, and a simpler test that can use a wet napkin is necessary.

The complete ascertainment of the frequency of phenylketonuria in the population requires the testing of all mental defectives. A simple and speedy test is very desirable.

If the ferric chloride test is used the urine should not be acidified.

A new test strip, phenistix, is a simpler and quicker method of testing urine for phenylpyruvic acid than methods hitherto used. It may also provide a partial answer to the problem of testing on the napkin. Unlike ferric chloride and 2:4-dinitrophenylhydrazine, it does not give a false-positive reaction with *p*-hydroxyphenylpyruvic acid, which has been found in the urine of a number of infants in the Cardiff survey.

We thank Sir George Pickering for providing laboratory facilities while the Population Genetics Research Unit's laboratories were being built; Professor A. G. Watkins for permission to refer to the phenylketonuric infant treated by him; Mr. R. A. Saunders for permission to quote his laboratory findings; Mrs. Philips, S.R.N., mental-health worker, Cardiff City Council, for her untiring assistance in collecting and testing the specimens of urine; and Ames and Co. for samples of "phenistix."

APPENDIX

Ames and Co. have produced "phenistix," a test strip which can be dipped into a specimen of urine and which indicates the presence of phenylpyruvic acid by turning green. Phenistix consists of a strip of thick absorbent paper, 6 by 0.4 cm., one end of which is impregnated with a ferric salt, a magnesium salt, and a buffer (cyclohexylsulphaminic acid). The stick can be compared with a colour chart on the bottle, giving the phenylpyruvic acid content of the urine. The usefulness of phenistix was investigated (cf. Rupe and Free, 1958; Baird, 1958).

The *p*H of a solution made by soaking phenistix in water was found to be 2.3, very close to the optimum *p*H for the reaction between ferric chloride and phenylpyruvic acid (cf. Berry and Woolf, 1952).

A specimen of urine from a child with phenylketonuria was used in preference to a synthetic standard. The specimen has been found, by the method of Berry and Woolf (1952), to contain 106 mg. of phenylpyruvic acid per 100 ml. Two dilution series were prepared: (i) with normal urine of about the same specific gravity, and (ii) with distilled water. Since the ratio of phenylpyruvic acid to total nitrogen is fairly constant, but urine from young infants is often dilute, (ii) probably represents the more important case. Each diluted specimen was tested with phenistix, with ferric chloride, and with 2:4-dinitrophenylhydrazine in 2N hydrochloric acid (saturated solution).

It was found that the phenistix strip had to be quickly dipped in and out of the urine; the reagents were leached out if the strip was left in the urine for much longer than a second or two. Maximum colour development occurred after one minute at a room temperature of about 20° C.—not after half a minute, the time recommended by the manufacturers for reading the strips. Unlike the ferric chloride test, the time to maximum colour development was independent of the temperature of the urine. For series (i), for a given concentration of phenylpyruvic acid, the colour on the strip corresponded closely to the colour on the chart; for series (ii) the strip was appreciably more bluish than the chart colour, though not so much so as to lead to uncertainty about the presence or absence of phenylpyruvic acid. The limit of detectability with phenistix for series (i) was 10 mg. per 100 ml., and for series (ii) it was 5 to 10 mg. per 100 ml.; with the ferric chloride test the limit of detectability was 5 mg. per 100 ml. for both series (i) and (ii); with 2:4-dinitrophenylhydrazine reagent the limit of detectability was 10 mg. of phenylpyruvic acid per 100 ml. of urine or aqueous solution. Thus all three tests have virtually the same sensitivity; urine from a phenylketonuric almost always has far more than 10 mg. of phenylpyruvic acid per 100 ml., about 100 mg. per 100 ml. being a usual value for children.

Reactions of Ferric Chloride and of Phenistix With Various Substances Added to Normal Urine

Substance	Phenistix	Ferric Chloride Solution
Phenylpyruvic acid ..	Blue-green, maximal in one minute, fading slowly	Blue-green. Eventually fades to yellow
p-Hydroxyphenylpyruvic acid	Ephemeral green, fading in 2–3 seconds	Blue-green.* Yellow with excess ferric chloride
Pyruvic acid	Golden yellow	Deep golden yellow
o-Hydroxyphenylpyruvic acid	Green*, maximal in about one minute	Initial red-brown turns green or blue*. Eventually fades to mauve
α-Ketobutyric acid ..	Faint brown-purple	Intense purple fading to red-brown in 1–2 seconds
"Maple syrup urine"†	Nil	Grey, with a greenish tinge
Sodium salicylate ..	Stable intense mauve	Stable intense mauve
Homogentisic acid ..	Nil (brown with stronger solution)	Fleeting green. Brown with stronger solution
o-Hydroxyphenylacetic acid	Very pale mauve	Mauve
3-Hydroxyanthranilic acid	Immediate yellow turns green* over one minute. Later brown	Immediate deep brown
Xanthurenic acid ..	Nil	Deep green*. Later brown
Vanillic acid	Brown	Red-mauve turning deep brown
Phenol	Nil	Deep blue-violet
Lysol	"	Green*
"Dettol"	"	Yellow

* Reaction difficult to distinguish from that of phenylpyruvic acid.
† Urine from a case of "maple syrup urine disease" (Mackenzie and Woolf, 1959).

A number of substances that might occur in urine, as rare endogenous products, or because of administration of drugs, or as contaminants, were examined, in solution in normal urine, for their ability to interfere with the ferric chloride and phenistix reactions. The results are shown in the Table.

Pieces of Turkish towelling, as used for babies' napkins, were wetted with urine from a phenylketonuric and a phenistix strip was applied. When the cloth was thoroughly wet, but not so wet that any urine could be squeezed or wrung out of it, a positive result was obtained on the strip, but only if the strip was placed between two layers of the wettest part of the cloth and firm pressure applied for several seconds. If the napkin was merely moist to the touch, as happens after a wet napkin is removed and allowed to stand for some hours, the strip was not moistened and no positive result was obtained. In this case a positive result could still be obtained as follows: the strip was dipped into water for the briefest possible moment and the wet end squeezed hard between the wettest parts of the napkin for several seconds; the buffered ferric salt dissolved and printed on to the napkin, where, if positive, a green patch appeared, the size and shape of the end of the strip. This technique was rather less sensitive to low concentrations of phenylpyruvic acid than the conventional one, and, owing to the different ratio of ferric salt and urinary substances, less specific, giving a green colour with *p*-hydroxyphenylpyruvic acid. It is a convenient way of applying buffered ferric salt to the napkin, and avoids the spreading effect of dropping ferric chloride solution on to it.

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ORAL TREATMENT OF PERNICIOUS ANAEMIA WITH VITAMIN B_{12} AND DESICCATED HOG DUODENAL EXTRACT

BY

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Oral administration of a substance with intrinsic factor activity is a rational approach to the treatment of pernicious anaemia. However, treatment by adequate parenteral vitamin B_{12} is so consistently effective in maintaining a normal state of the blood and bone marrow, and in safeguarding against the development of neurological complications, that any other form of therapy must be shown to be as effective before it can supplant injections of vitamin B_{12} in the routine management of the disease. Oral therapy has an obvious attraction, and Wilkinson (1949) has shown that excellent results may be obtained by the use of a relatively crude preparation of desiccated hog's stomach. In recent years preparations have been used in the treatment of pernicious anaemia containing, in tablet form, a small amount (5–15 μg.) of vitamin B_{12} and an extract of desiccated hog duodenal or pyloric mucosa. Evidence has been accumulating that this form of therapy usually results in a good initial response, but with continued treatment haematological remission and normal levels of vitamin B_{12} in the serum are not maintained (Bastrup-Madsen, 1957; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Killander, 1958). It has been shown that many patients treated with such oral preparations ultimately have reduced intestinal absorption of vitamin B_{12} when hog pyloric mucosa is supplied as intrinsic factor (Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Stokes and Pitney, 1958). This leads ultimately to deficiency of vitamin B_{12} and clinical relapse.

The present report describes the results of treatment of pernicious anaemia patients with "biopar" tablets over a period of five years, and is an extension of a previous report on treatment with biopar for one year (Blackburn *et al.*, 1955). The changes in the peripheral blood, the bone marrow, and the levels of vitamin B_{12} in the serum have been followed during this period of treatment. In addition, tests were made for skin sensitivity to hog intrinsic factor prepared by the same method as used in biopar tablets.

Patients Studied and Details of Treatment

The results of oral treatment with tablets containing crystalline vitamin B_{12} and a desiccated extract of hog duodenal mucosa (biopar and biopar forte) have been studied in 22 patients with Addisonian pernicious anaemia. In all cases the diagnostic criteria included megalocytic anaemia, megaloblastic erythropoiesis in the bone marrow, histamine-fast gastric achlorhydria, and the absence of evidence of steatorrhoea or other recognized cause of megaloblastic anaemia. Each tablet of biopar contained 6 μg. of vitamin B_{12} and 30 mg. of the intrinsic factor preparation; each tablet of biopar forte contained 15 μg. of vitamin B_{12} and 35 mg. of the intrinsic factor preparation.

Thirteen patients (Cases 1–13) who had previously been treated with parenteral vitamin B_{12}, and in whom steady and normal levels of haemoglobin and red-cell count had been maintained during at least one year, were transferred to treatment with biopar in November, 1953. From then until June, 1955, these patients received one tablet of biopar daily. The dose was then increased to two tablets daily until October, 1956. In 1956 the production of biopar tablets was stopped, and they were replaced by biopar forte. From October, 1956, until March, 1959, treatment was given with biopar forte, two tablets daily.

Nine patients with previously untreated pernicious anaemia who had shown a satisfactory initial response to oral treatment were included in the study. Four of these patients (Cases 14–17) were given initially five tablets of biopar daily. This was continued for two to nine months, until June, 1955, when they were transferred to the above scheme of dosage. Five patients (Cases 18–22) received biopar forte, five tablets daily for six months, and then continued treatment with two tablets daily.

The results during the first year of treatment with biopar in 10 of these patients have already been published (Blackburn *et al.*, 1955). Of the 22 patients included in the present study, five did not complete the trial for reasons detailed below.

Methods of Investigation

In all cases determinations of haemoglobin level (M.R.C. grey wedge photometer; oxyhaemoglobin—

100% = 14.8 g./100 ml.) and standard red-cell count were made every four to eight weeks.

Biopsy of iliac bone marrow was performed in 13 patients after treatment with biopar for 3½ years, and in nine patients further marrow examination was made at the end of five years of oral therapy.

The concentration of vitamin B_{12} in the serum was estimated after treatment with biopar for 2½, 3½, and 5 years. In five patients this estimation was carried out before starting therapy and again after treatment with biopar for six to 13 months. The amount of vitamin B_{12} in samples of serum was estimated by microbiological assay, using *Lactobacillus leichmannii* as the test organism (Spray, 1955).

Skin-testing was carried out with an extract of hog pyloric mucosa, as contained in biopar tablets. In each test, 0.02 ml. of a 1/100 dilution of the extract in normal saline was injected intradermally on the front of the right forearm. A control injection of 0.02 ml. of normal saline was also given on the left forearm.

Results

The levels of haemoglobin and red-cell count during the first year of treatment with biopar in 12 patients formed the subject of a previous publication (Blackburn *et al.*, 1955). Of these 12 patients, two were not included in the subsequent study. One died of pneumonia soon after the end of the first year; peripheral blood examination had been within normal limits a few weeks before death. The other patient developed persistent paraesthesiae in the hands at the end of the first year, without objective signs of neurological abnormality and without abnormality of the blood. Nevertheless, treatment with biopar was stopped and injections of vitamin B_{12} were recommenced. There was little symptomatic change after parenteral vitamin B_{12} therapy, and it now seems unlikely that any neurological changes due to vitamin-B_{12} deficiency had been present. Two other patients died during the subsequent study: one (Case 13) died of coronary thrombosis after three years, and the other (Case 6) died of carcinoma of the prostate after four years of treatment with biopar. In each of these cases the last haemoglobin estimation, red-cell count, and blood film, made within a few weeks of death, were normal.

Haematological relapse occurred in three patients out of a total of 17 after treatment with biopar for 2½ to 5 years. These patients were believed to be reliable, and they stated that they had taken the prescribed tablets regularly.

Case 1.—This patient, who had previously received parenteral therapy with liver extract and later vitamin B_{12} for a total of seven years, showed a persistent fall in red-cell count to about 3,600,000/c.mm., associated with macrocytosis in the peripheral blood film after treatment with biopar for five years. The level of vitamin B_{12} in the serum at this time was 65 μμg./ml. and the bone marrow showed the typical appearances of vitamin-B_{12} deficiency in the red-cell and white-cell precursors. There was a prompt return of the blood to normal after the resumption of parenteral vitamin-B_{12} therapy.

Case 3.—Previous treatment with liver extract and later vitamin B_{12} had been given for a total of six years. After treatment with biopar for 3½ years the red-cell count, which had previously been maintained above 4,500,000/c.mm., showed a persistent fall, reaching 2,500,000/c.mm., and the peripheral blood film contained many macrocytes. The bone marrow showed megaloblastic erythropoiesis. The concentration of vitamin B_{12} in the serum at this time was 30 μμg./ml. Parenteral therapy with vitamin B_{12} was followed by an increase in the red-cell count to 5,300,000/c.mm. in one month.

Case 14.—This patient, with previously untreated pernicious anaemia, had initially shown an adequate haematological response to biopar. However, after treatment with biopar for 21 months the level of vitamin B_{12} in the serum was 56 μμg./ml., and seven months later it was 10 μμg./ml. At this time the red-cell count began to fall and reached 2,900,000/c.mm., the bone marrow showing megaloblastic erythropoiesis. After parenteral therapy with vitamin B_{12} the red-cell count returned to normal.

Two other patients (Cases 2 and 4) showed a fall in haemoglobin level and in red-cell count while on biopar therapy. In both cases the appearances of the peripheral blood film suggested concomitant iron deficiency, and the blood returned to normal when oral treatment with iron was given in addition to biopar.

In the remaining 12 patients in this series the levels of haemoglobin and red-cell count have remained within the normal range during the period of biopar treatment. Statistical analysis of all the red-cell counts made during the entire period of treatment in these cases has not revealed any significant trend. In no case did neurological signs develop during biopar treatment.

Examination of the bone marrow was made after treatment with biopar for 2½ to 3½ years in 13 patients (Table I); typical megaloblasts were present in two

TABLE I.—*Levels of Vitamin B_{12} in Serum and the Appearance of Bone Marrow During Treatment with Biopar in 17 Patients With Pernicious Anaemia*

Case No.	Age and Sex	Serum Level of Vitamin B_{12} (μμg./ml.) after Treatment with Biopar for			Evidence of Vitamin-B_{12} Deficiency in Bone Marrow	
		2½ Yrs.	3½ Yrs.	5 Yrs.	3½ Yrs.	5 Yrs.
1	69 F	160	35	65	+	++
2	74 F	280	240	250	0	+
3	78 M	140	76	30 (4yr.)	++	–
4	73 F	270	90	65	+	++
5	75 F	190	110	100	0	–
6	82 M	180	120	–	–	–
7	82 M	78	19	35	+	++
8	70 F	210	75	140	+	–
9	50 F	220	120	170	0	0
10	89 F	110	84	72	+	–
11	52 M	–	32	40	0	0
12	53 F	590	430	290	–	–
13	65 M	110	–	–	–	–
14	78 F	10	–	–	++ (2½ yr.)	–
15	58 F	130	69	100	+	0
16	42 F	220	–	170	–	++
17	41 M	460	340	830	0	0

The results of marrow biopsy are classified in three categories: no evidence of vitamin-B_{12} deficiency, (0); slight abnormalities consistent with but not diagnostic of vitamin-B_{12} deficiency, (+); evidence of vitamin-B_{12} deficiency, (++).

(Cases 3 and 14), who therefore were treated subsequently with parenteral vitamin B_{12}. In six there were minor abnormalities suggestive but not diagnostic of vitamin-B_{12} deficiency, and in the remaining five the marrow appeared normal. Bone-marrow examination after treatment with biopar for five years showed megaloblasts typical of vitamin-B_{12} deficiency in four of nine cases. Thus within five years megaloblasts were present in at least 6 out of 17 cases.

The results of estimations of vitamin B_{12} in the serum are shown in Table I. By the method used the normal range is 150–1,000 μμg./ml. (Spray and Witts, 1958). After treatment with biopar for 2½ years the level of vitmain B_{12} in the serum was less than 150 μμg./ml. in 6 out of 16 cases, and after treatment for 3½ years the level was abnormally low in 11 cases. It is noteworthy that, in the patients in whom the concentration of vitmain B_{12} in the serum was normal after treatment

with biopar for 3½ years, the level was still within the normal range after treatment for five years.

In the nine cases (Nos. 14–22) of hitherto untreated pernicious anaemia, treatment with biopar resulted in a satisfactory initial response. The increase in red cells in 14 days was very similar to the "average response" to potent liver extract (Della Vida and Dyke, 1942),

TABLE II.—*Levels of Vitamin B_{12} in Serum in Five Patients With Pernicious Anaemia Before Starting Treatment, and After Treatment with Biopar Tablets for 6 to 13 Months*

Case No.	Age and Sex	Serum Level of Vitamin B_{12} ($\mu\mu$g./ml.)		Duration of Treatment with Biopar (Months)
		Before Treatment	After Treatment with Biopar	
18	60 F	20	200	13
19	63 F	22	250	9
20	76 F	25	88	6
21	70 F	52	52	8
22	62 F	30	92	9

except in one case, in which there was evidence of concomitant iron deficiency; a reticulocyte response of 32% (dry method) followed the start of biopar therapy, but the increase in red cells was at first slow. When iron by mouth was added the red-cell count rapidly increased to normal. However, when the level of vitamin B_{12} in the serum was estimated in five of these patients after treatment with biopar for 6 to 13 months, it was within the normal range in only two (Table II).

Skin tests by intradermal injection of a 1/100 dilution of an extract of hog pyloric mucosa were carried out in 13 patients after treatment with biopar for four to five years. For comparison, skin tests were performed, using the same technique and preparation of hog pyloric mucosa, in 16 patients with pernicious anaemia who had been treated for 2 to 20 years with liver or vitamin-B_{12} injections, and who had never received biopar tablets or other oral preparation for the treatment of pernicious anaemia. A slight positive reaction was observed in three of the biopar patients; in two of these the level of vitamin B_{12} in the serum was abnormally low (Cases 11 and 21), and in one it was normal (Case 12). The reaction consisted of an area of erythema about 1 cm. in diameter, observed 15 to 30 minutes after injection, with no reaction to the control injection. In no patient was there any weal formation or pruritus. A similar slight positive reaction was observed in 2 of the 16 patients with pernicious anaemia who had never received biopar.

Discussion

The results of this study show that neither biopar nor biopar forte is reliable in the treatment of pernicious anaemia. In the group of patients who had been well maintained previously by parenteral vitamin B_{12} the levels of vitamin B_{12} in the serum became abnormally low in 11 out of 14, after treatment with biopar for 3½ years. In two of these patients there was a reduction in red-cell count with clinical relapse after 3½ to 5 years of biopar therapy. The patients with previously untreated pernicious anaemia showed a satisfactory clinical and haematological response at first to biopar treatment, but in several cases the level of vitamin B_{12} in the serum was abnormally low after six to nine months, and in one patient there was haematological relapse after 2½ years. One case has previously been reported in which there was a failure of initial response to biopar but subsequent good response to parenteral vitamin B_{12} (Blackburn *et al.*, 1955). These results with biopar are very similar to the published results with other oral preparations containing a small amount of vitamin B_{12} along with an extract of hog pyloric mucosa—"bifacton" (Mollin and Ross, 1954; Killander, 1958), "bendogen" (Berlin *et al.*, 1958), and "cycoplex" (Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957). As with these other oral preparations, increasing the dose of biopar did not prevent relapse.

The haemoglobin concentration and red-cell count remained normal for up to at least two years after the level of vitamin B_{12} in the serum had been found to be abnormally low; a similar time lag in haematological relapse was reported by Killander (1958), and it is clear that satisfactory levels of haemoglobin and red-cell count over a period of years in a patient with pernicious anaemia is not proof that the treatment given is adequate in preventing vitamin-B_{12} deficiency.

The failure of oral preparations containing vitamin B_{12} and hog pyloric mucosa to maintain remission in pernicious anaemia after an initial good response appears to result from a late development of a block in the intestinal absorption of vitamin B_{12}. When refractoriness to these oral preparations develops, labelled vitamin B_{12} is not absorbed when given orally along with hog pyloric mucosa, but is well absorbed when given with normal human gastric juice (Killander, 1957; Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Berlin *et al.*, 1958; and Stokes and Pitney, 1958). Taylor and Morton (1958) have produced specific rabbit antisera which can neutralize human or pig intrinsic factor activity, and Schwartz (1958) has shown that the serum of some patients treated with oral preparations of vitamin B_{12} and hog pyloric mucosa has the property of inhibiting intrinsic factor. This cannot explain all the observed phenomena in pernicious anaemia treated by oral preparations, as the inhibitory activity was observed against human intrinsic factor as well as hog pyloric mucosa.

The skin tests performed with the extract of hog duodenal mucosa failed to demonstrate any relationship between skin sensitivity to the extract and relapse of pernicious anaemia during treatment with biopar. Although two patients who had low levels of vitamin B_{12} in the serum after treatment with biopar showed a slight positive reaction, a similar response was obtained in one biopar patient who had a normal level of vitamin B_{12} in the serum and in two patients with pernicious anaemia who had never received biopar.

Small daily oral doses of vitamin B_{12} without added intrinsic factor may produce haematological response in some patients with pernicious anaemia (Estren and Wasserman, 1956; Chalmers and Shinton, 1958), and it is possible that the initial response to biopar reported above in previously untreated cases of pernicious anaemia may have resulted entirely from the vitamin-B_{12} content of the tablets. The patients with previously untreated pernicious anaemia in the series now reported received, in the biopar tablets, 30–75 μg. of vitamin B_{12} daily for up to nine months. Chalmers and Shinton (1958) have shown that 50 μg. of vitamin B_{12} daily, given orally, produced haematological response, but did not maintain normal levels of vitamin B_{12} in the serum, whereas 100 μg. of vitamin B_{12} daily by mouth resulted in normal levels of vitamin B_{12} in the serum.

Summary

Oral treatment of pernicious anaemia with "biopar," a preparation containing vitamin B_{12} and an extract of

hog duodenal mucosa, has been studied in 22 patients. Thirteen patients who had previously been treated satisfactorily with parenteral vitamin B_{12} for at least one year, received biopar therapy for up to five years. After 3½ years the level of vitamin B_{12} in the serum was abnormally low in most patients, and haematological relapse occurred in two patients after four to five years.

Nine patients with previously untreated pernicious anaemia showed a satisfactory initial response to biopar therapy, but one relapsed after 2½ years and in four others the vitamin B_{12} in the serum did not reach a satisfactory level. The level of vitamin B_{12} in the serum reached the normal range in the remaining four, in two of whom normal values were still found after treatment for five years.

Skin tests performed with an extract of hog duodenal mucosa did not show any relationship between skin sensitivity to the extract and refractoriness to biopar treatment.

The results of the investigation show that this oral treatment is not reliable for maintenance of patients with pernicious anaemia.

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The polio vaccination campaign among young people is being intensified in two of the L.C.C.'s health divisions in north London. Dr. J. A. SCOTT, the L.C.C.'s Medical Officer of Health, has written to nearly 10,000 firms, coffee bars, dance halls, hairdressers, gramophone record shops, and others in Finsbury, Hackney, Holborn, Islington, Shoreditch, and Stoke Newington to ask for their help. In Finsbury, Holborn, and Islington the council will use a mobile clinic to take "the jab to the job," parking in or near the factories and offices where the young people work. Up to September this year there have been 84 confirmed cases of polio in these six north London boroughs, six of them fatal. But Dr. Scott points out that quite three-quarters of young Londoners between the ages of 15 and 26 have not yet sought protection: this despite the fact that the chances of being attacked by polio are about five times greater for the unvaccinated than for the vaccinated.

PLACENTAL IMPLANTATION FOR PERIPHERAL VASCULAR DISEASE

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Since Filatov (1935) reported the use of various tissue implants as an aid in corneal grafting, numerous papers have been published from the continent of Europe advocating placental tissue or placental extract in the treatment of many diseases. Sneep (1955) from Holland, and Piccoli (1954) and Cordaro (1957) from Italy, have recommended this therapy for advancing the healing of wounds and ulcers, while in the German literature several reports have appeared on the use of placental extract in the disturbances of the climacteric (Branger and Krattiger-Müller, 1957). The extract has also been used in skin wounds by Bromilski (1956), of Poland, and in intestinal fistula by Junod (1954), of France. In this country Troensegaard-Hansen (1956) has used amnion both as an implant and as a surface application for ulcers.

In 1956 D. Le Grand (personal communication) stated that implantation of the cotyledon surface of the placenta gave spectacular results in persistent intermittent claudication, and the present paper is a favourable preliminary report of a clinical trial of this method of treatment.

Method

Selection of Patients.—Every patient reporting to the clinic on account of severe intermittent claudication was admitted for investigation and included in the first part of this trial. Later, the method was attempted on an out-patient basis. These patients had previously had Buerger's exercises, and in many cases had received vasodilator drugs. A few had had a previous sympathectomy. Each patient was warned that two implants might be required, so that a control series could be arranged. If the control method of treatment failed, the patient received an implant of placenta.

Assessment of the Patients.—A full history and medical examination revealed the general state of the patient. Examination of the cardiovascular system was supplemented in most cases by an electrocardiogram and ophthalmoscopy. The peripheral circulation was assessed by inspection of the skin, palpation of the pulses, estimation of venous filling time, and exercise tolerance. The actual lesion was identified by arteriography, which also gave an indication of the collateral circulation and general state of the vessels. The capacity of the arteries to dilate was assessed by a reflex heating test and the blood flow in the limbs by oscillometry. This assessment enabled the patient to be placed in one of three groups suitable for: (1) conservative treatment, (2) sympathectomy, or (3) arterial graft. Patients in all three groups received placental implants as the first method of treatment.

Preparation of Placenta.—A placenta was delivered straight from the maternity unit in a sterile container. The blood group of mother and placenta was

established. Under full aseptic precautions a number of 1-cm. cubes of the cotyledon surface were excised, and each cube was placed in a universal container with 1 mega unit of penicillin dissolved in 4 ml. of normal saline. These containers were incubated at 4° C. for five days, when the tissue was considered ready for implantation. Three 1-cm. cubes were implanted subcutaneously in the thigh of the maximally affected limb, through small separate incisions.

Control Series.—The patients were divided by random selection into five groups, only one of the authors knowing to which group the patients belonged. Group 1 received an implant of placenta. Group 2 received an "implant" of penicillin and saline to act as controls for the trauma of incision and for the use of preparation fluid. Group 3 received an "implant" of the preparation fluid after it had been incubated with the placental tissue for five days. This method produced a saline extract of the placenta. Group 4 received an "implant" of similarly prepared human protein, thereby acting as a foreign-body protein. Group 5 received an "implant" of 150 mg. of ethinyloestradiol.

Assessment of Results.—The patients were examined at intervals in the immediate post-operative period, and, in particular, the reflex heating test and oscillometry were repeated five days after implant.

After discharge from hospital the patients were seen regularly by various members of the staff.

Clinical Features

TABLE I.—*Age and Sex Incidence*

	Age in Years					
	40–	50–	60–	70–	80–	90–
Males	3	9	10	6	1	1
Females	2			5		

Age and Sex Incidence (Table I).—62% of the patients were over 60, and the sex ratio was approximately three males to every female.

Symptoms

Intermittent Claudication (Table II).—This was the main symptom, and the severity was graded as: severe = less than 100 yards; moderate = less than 440 yards; mild = more than 440 yards. The majority of the patients were in the severe grade: 60% had a history of claudication for over two years. It was interesting to note that the right leg was affected more frequently than the left.

TABLE II.—*Pain*

Side		Duration		Severity	
Left	6	< 6 months	8	Severe	27
L > R	8 } 14	6/12–1 year	4	Moderate	9
		1–2 years	2	Mild	1
Right	8	2–5 ,,	13		
R > L	10 } 18	5–10 ,,	5		
L = R	5	10–20 ,,	5		

Associated Symptoms (Table III).—Evidence of coronary arterial disease was common, six patients subsequently developing coronary thrombosis and four dying with myocardial infarction.

TABLE III.—*Associated Symptoms*

Angina of effort	12
Dyspnoea on exertion	11
Previous coronary thrombosis	4
Varicose veins	4
Near gangrene }	5
Necrotic ulcer }	
Diabetes mellitus	2

Signs

Peripheral Pulses (Table IV).—The right popliteal pulse was absent more often than the left, which agreed with the frequency of the complaint of pain in the right side.

TABLE IV.—*Pulses Palpable*

Artery	Right	Left
Femoral	35	36
Popliteal	17	23
Anterior tibial	12	11
Posterior ,,	11	10
Dorsalis pedis	12	7

Severe Trophic Changes.—In two cases there were chronic ulcers on the leg, which failed to respond to conservative therapy and were thought to be due to inadequate arterial circulation. Four cases had incipient gangrene, and three of these eventually required amputation.

Blood Pressure. — Most of the patients were hypertensive.

Venous Filling Time (Table V).—This test confirmed the diminution of flow in the more affected leg and was considerably prolonged in three-quarters of the group.

TABLE V.—*Venous Filling Time*

	< 15 Seconds	< 30 Seconds	> 30 Seconds
Better leg	7	11	3
Worse ,,	5	6	10

Electrocardiography.—Eleven out of 33 patients had evidence of a damaged myocardium, which confirmed the clinical evidence of a history of previous infarction or angina pectoris.

Reflex Heating Test.—This was done on 34 patients and only eight showed a good response to the test. It was interesting to note the flat curves of patients who had previously had a sympathectomy. In these cases the initial temperature level was higher on the sympathectomized side.

Oscillometry.—This was carried out in the first 28 patients investigated. Only six had normal readings; the remainder showed evidence of severely diminished blood flow in the affected limb. The test was not used routinely for the rest of the series.

Arteriography.—Fourteen of the initial series showed a localized block, and in seven the disease was found to be a diffuse atheroma.

Blood Group.—The blood-group distribution was almost identical with figures for the South-Eastern Region of Scotland, and was insignificant in this series.

Results

Group 1, Placental Implant (Table VI)

TABLE VI.—*Results*

	Subjective	Oscillometry	Reflex Heat
Group 1:			
Initial series	19/28	2	7
Total ,,	27/39		
Group 2	0/5	0	0
,, 3	3/5	1	1
,, 4	0/3	0	0
,, 5	3/8	0	1

Thirty-nine patients received placental implants, and of these 27 felt a noticeable effect. Following implant, there was a definite pattern of response. Within six hours the patient usually experienced a feeling of

tingling and heat in both lower limbs. Subsequently, the exercise tolerance increased, as measured by the claudication distance.

In the follow-up period, some of the patients who had responded relapsed after some months and had a repeat implantation. These patients again experienced improvement in their symptoms. Fig. 1 indicates the duration of the improvement and the fact that in over two-thirds of the patients it was prolonged over six months.

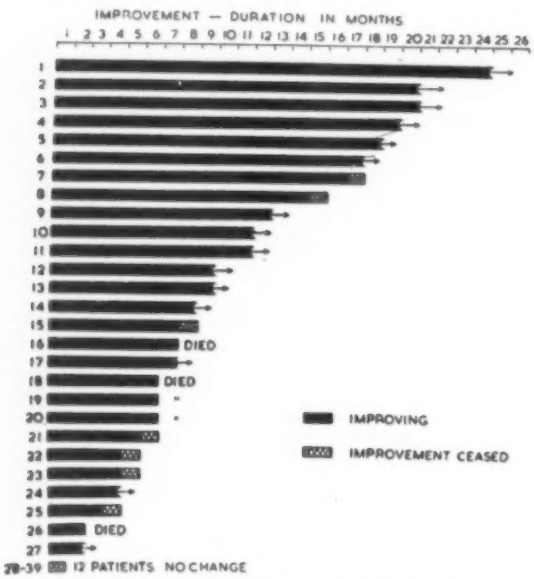
IMPROVEMENT — DURATION IN MONTHS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
DIED
DIED
IMPROVING
IMPROVEMENT CEASED
DIED
12 PATIENTS NO CHANGE

FIG. 1.—Duration of improvement in symptoms.

Clinical examination revealed an apparent increased skin temperature, but there was no change in the peripheral pulses. In four patients, two with early infective necrosis of toes and two with long-standing ulcers over the medial malleolus, otherwise resistant lesions healed and remained healed.

Investigation showed an improvement in the reflex heating response in 7 out of 28 cases, but an improvement in the oscillometry readings was noted in only 2 of the 28.

Groups 2-5 Controls (Fig. 2)

Patients in group 2 and group 4 showed no change, but three of the five cases in group 3 had a temporary improvement in their claudication distance. Group 5 cases also showed some improvement for a short time, three out of eight responding to the implantation of oestrogen hormone.

Discussion

This investigation into the effect of placental implantation in patients with peripheral vascular disease was planned to discover — (*a*) if it caused any improvement in the patient's symptoms, (*b*) if the improvement was subjective or if objective evidence of improvement could be obtained, and (*c*) If an obvious cause could be found for improvement when it occurred.

From the results obtained it was clear that most patients did obtain some relief of their symptoms, especially as judged by their claudication distance. It is realized that the estimation of walking distance without carefully controlled treadmill conditions may be misleading, yet the effect was so striking and appeared in such a short time that it seemed to be convincing.

The subjective feeling of increased warmth in the limbs noted by all patients who were in the improved group was accompanied by a rise in the skin temperature, with a better response to the reflex heating test in 7 out of 28 cases. Despite this, however, oscillometry showed an improvement in only 2 out of 28 cases, and in no case was any alteration in pulses noted.

FIG 2.—Results in groups 2-5. Key as Fig. 2.

That the collateral circulation is not obviously improved is suggested by the fact that of five patients who had deteriorated despite previous lumbar sympathectomy placental implantation gave a good result in only two, while of three patients who failed to respond to placental implant sympathectomy relieved only one patient, the other two showing no improvement from either form of treatment.

The possibility that any effect is due to a non-specific reaction to foreign protein introduced in the placental tissue seems unlikely, since patients in Group 2 showed no beneficial response of any duration.

The fact that the injection of the fluid in which the placental tissue had been stored for five days gave a satisfactory, if temporary, response suggests that there is some substance in placenta which is responsible for the effect, and that this effect lasts longer when active placental tissue is implanted. The nature of the substance has not yet been determined, but from the effect of 150 mg. of ethinyloestradiol it is tempting to associate it with this hormone.

Urinary gonadotrophin excretion was assayed in one patient who gave a good response to the implant of placenta, and this showed no change in levels.

In two cases the placental implant was removed after amputation and had remained viable after seven days. In cases with remission of symptoms it was noted that the longer the implants remained palpable the longer was the relief of symptoms.

In five patients who had a good effect from the first placental implant a second implant was made, and in three the satisfactory response was repeated (Fig. 3). This again suggests that an active principle is secreted by or liberated from the placental tissue which is responsible for the effect.

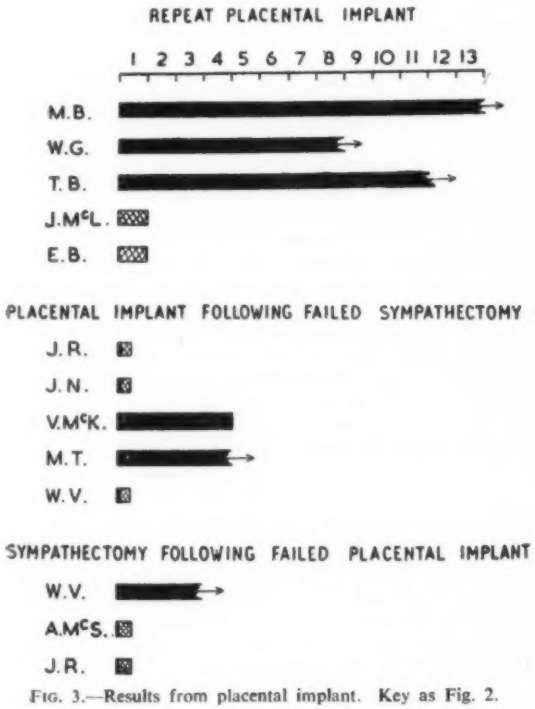

FIG. 3.—Results from placental implant. Key as Fig. 2.

In this investigation arteriograms were carried out in each patient, and 14 showed a localized block in the worst-affected limb. Nine of these patients were on general grounds unfit for any major surgical procedure, a tenth had additional gross atheroma, while a further patient had a block in the popliteal fossa, with no filling of the collateral vessels. Thus only three of this series of patients could be regarded as suitable for arterial grafting. The remainder of the series showed generalized atherosclerosis, and since this investigation was begun two years ago six have died as a result of myocardial infarcts or cerebrovascular accidents.

Sympathectomy was considered in all cases in which placental implant failed to improve the condition of the skin, but only 8 out of 34 patients tested by reflex heating showed a good response, and, of these, only three were regarded as good operative risks.

In conclusion, this investigation seems to have established that placental implant causes subjective improvement in the patient's symptoms and has a useful place in the treatment of peripheral vascular disease. The active principle is not yet known, and is a matter for further investigation.

Summary

A controlled investigation into the effect of placental implant in peripheral vascular disease was carried out.

Placenta, placental extract, and implantation of ethinyloestradiol produced relief of symptoms for varying periods.

Foreign protein, or saline and penicillin, inserted under identical conditions, produced no remission of symptoms.

There is some indication that the favourable effects are due to placental hormones, possibly those of the oestrogen group.

We acknowledge the help given by Dr. Lorraine, of the Clinical Endocrinology Research Unit, who undertook the assay of the placental hormones and of the gonadotrophin in this investigation.

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An international panel of experts, convened by the International Atomic Energy Agency to study the best methods of collecting and measuring trace amounts of radioactive substances present in the biosphere (man's surroundings), met in Vienna from September 7 to 12. The rapidly increasing use of radioactive materials for peaceful purposes is confronting many countries with the necessity of introducing a system of collection and accurate measurement of radioactivity, both natural and artificial, in the biosphere. This will serve as a means of checking whether or not small amounts of radioactive substances from reactors, for instance, or from industrial processes, are reaching the soil, rivers, or the atmosphere. Such systematic measurement could be used as the basis for controls to forestall any dangers to health and property. The I.A.E.A. panel hopes to issue recommendations as to the best methods of collecting samples and of measuring their radioactivity. (International Atomic Energy Agency, Vienna.)

TREATMENT OF TAPEWORM INFECTIONS IN MAN

BY

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Remarkably little information is available on the efficacy of different anthelmintic regimes under standard conditions; assessment of their relative merits is therefore difficult or impossible. In an effort to supply this need, detailed observations have been made on all patients treated for tapeworm infections at the Hospital for Tropical Diseases, London, during the past eight years. The series comprises 240 patients distributed into five main treatment groups, the numbers in each of which are now such as to permit an adequate statistical analysis.

Clinical Material and Methods

Of the 240 patients, 238 were infected with *Taenia saginata*, one with *Taenia solium*, and one with *Dibothriocephalus latus*. There were seven children in the series, all infected with *T. saginata*.

Several methods of treatment were used in chronological sequence, and, as a preliminary to each, all food was withheld from the patients for a period which during the earlier years of the study was usually three days, but which later was reduced to two days. During the period of fasting, patients were allowed only bland fluids other than those containing milk, and a small saline purge was administered each morning. If the head of the worm was not immediately recovered, patients were followed up for at least four months before they were regarded as cured.

Treatment Regimes

Oral Administration of Male Fern.—Two mixtures of male fern were used. The first consisted of 8 ml. of extract of male fern, 8 g. of acacia, and cinnamon water to 42 ml.; in the second, to the same constituents 14 ml. of glycerin was added. The dose of male fern was reduced to 6 ml. for adults weighing less than 60 kg., to 4.6 ml. for one child of 12 years, to 4 ml. for two children between 4 and 7 years, and to 2.4 ml. for one child aged 3 years 11 months. "Ribena" was used as a flavouring agent for the young children. In all cases the total dose was divided into three and administered at 15-minute intervals, followed in a further 30 minutes by a saline purge. The mixture containing glycerin was given to 59 patients and that without it to 33. The results of treatment in these two groups have been analysed separately.

Administration of Male Fern by Duodenal Intubation.—The patient lay on the right side after swallowing 65 cm. of Rehfuss tube, and two to three hours later material aspirated through the tube was tested with Congo red. If it was alkaline the tip of the tube was assumed to be in the duodenum, and this assumption was strengthened if, after oral administration of a small quantity of very dilute gentian-violet solution, material immediately aspirated was free from violet colouring. Male fern was administered through the tube either as the plain extract or in the form of a mixture with glycerin (see above). The results have not been analysed separately. The second method was found to be the simpler of the two, for the viscosity of the plain extract caused it to adhere to the inside of the tube, and this and the internal volume of the tube made it necessary to administer 15 ml. from the syringe in order to deliver 8 ml. from the end of a medium-sized Rehfuss tube. The tube must be swallowed empty if the patient is not to experience the unpleasant flavour of the anthelmintic. It is therefore important to ascertain the amount which must be injected into it in order to fill it and deliver a given amount at its extremity. Failure to attend to this point may well have been responsible for some of the failures ascribed to the drug in the literature. An alternative would be to inject only the amount of the dose and to wash it through the tube with water or other solvent. The undiluted extract, however, is sufficiently viscid to cause an undetermined quantity to remain even after an undesirably large amount of water has been injected into the tube. As with oral treatment, adults weighing less than 60 kg. and also three children aged 12–14 were given 6 ml. of male fern. The tube was removed immediately after delivery of the anthelmintic, and a saline purge was given 30 minutes later. This regime was employed in 52 cases.

Oral Administration of Mepacrine.—A solution of 1 g. of mepacrine in 42 ml. of water was swallowed over the course of an hour by 49 patients, and a saline purge was given 30 minutes later.

Administration of Mepacrine by Duodenal Tube.—To 26 patients 1 g. of mepacrine dissolved in 42 ml. of water was administered by a duodenal tube through which a saline purge was given half an hour later.

Oral Mepacrine and Male Fern.—To 21 patients 0.3 g. of mepacrine dissolved in 20 ml. of water was given in the evening after the usual period of fasting. This was followed by a similar dose early the next morning, and three hours later an emulsion of male fern was given according to the method of administering it outlined above.

All stools on the day of treatment were passed into a bedpan containing a little water. After treatment with male fern it was usually necessary to search for the head of the worm, as in most cases the worm was passed in separate sections; the search was facilitated by the fact that the preliminary starvation had caused the bowel to become empty of faeces. After successful treatment with mepacrine the worm was invariably passed intact a few hours later, and was bright yellow in colour. It is considered important to search for the head of the worm, for when it is not found the patient can be told that a cure can be presumed only if segments do not reappear within three to four months. Without such a follow-up scheme no conclusion can be drawn on the effectiveness of treatment, for in only 60% of the patients under review could the head of the worm be identified after treatment.

Results

Of the 240 patients, 189 (78.7%) were cured by a single course of treatment; 144 (76%) of these passed the head of the worm, and in 45 (24%) it was possible to presume cure as no segments appeared in the stools during the follow-up period. When treatment failed, segments reappeared, on average, 10 weeks later (range 4 to 16 weeks). All seven children in the series were treated with male fern—four orally and three by

duodenal tube—and there were two failures among them. In both these children, aged 12 and 3 years 11 months respectively, male fern was administered orally in dosages which we would now regard as suboptimal. Among the 240 patients two heads were found on four occasions, giving an incidence of double infection with *T. saginata* of 1.6%. The patients infected with *T. solium* and *D. latus* were successfully treated orally with the mixture of male fern containing glycerin. In two patients a concomitant infection with *Giardia lamblia* was found at the time of treatment; mepacrine administered by mouth was successful in eradicating the infection in one and mepacrine by duodenal tube was equally successful in the other.

The results obtained with the five methods of treatment are recorded in the Table. Statistical analysis showed that, with the numbers of patients involved, the differences between them are no more than might easily arise by chance.

Results Obtained With the Various Treatment Regimes

Method	Total	Cured	Doubtful	Failed	Failure Due to Vomiting*
Oral male fern in an emulsion without glycerin	33	24 (73%) H.F. 17 (71%) F.U. 7 (29%)	2 (6%)	7 (21%)	1
Oral male fern in an emulsion with glycerin	59	48 (81%) H.F. 44 (92%) F.U. 4 (8%)	2 (3%)	9 (15%)	2
Male fern by tube	52	42 (80%) H.F. 23 (55%) F.U. 19 (45%)	6 (12%)	4 (8%)	2
Oral mepacrine	49	39 (80%) H.F. 33 (85%) F.U. 6 (15%)	2 (4%)	8 (16%)	5
Mepacrine by tube	26	23 (88%) H.F. 21 (91%) F.U. 2 (9%)	1 (4%)	2 (8%)	1
Oral mepacrine and male fern	21	13 (62%) H.F. 6 (46%) F.U. 7 (54%)	2 (10%)	6 (28%)	2
Total ..	240	189 (79%)	15	36	13

H.F.=Head found. F.U.=Proof of cure obtained by follow-up. *In patients included in the preceding column.

Discussion and Conclusion

The main conclusion which may be drawn from these studies is that treatment with the different drugs and regimes used has given very similar results. It may thus fairly be stated that under the conditions of this study—namely, the patient being admitted to hospital and denied food for at least 48 hours before treatment—extract of male fern and mepacrine in the dosages used are of equal value as anthelmintics. Adequate fasting is thought to be a valuable preliminary to anthelmintic treatment, for not only does it facilitate contact between the anthelmintic and the worm, but also it renders the head of the worm, if passed, easier to identify than when it must be searched for amid a mass of faecal material. Among those treated by the various methods here employed and who fasted for 72 hours, 84.3% were cured with a single course of treatment, whereas among those who fasted for less than this period 74.5% were cured. The standard error of the difference between these proportions is 5.56 and the actual difference 9.8; thus, although the difference is not strictly statistically significant, it is near the point at which it becomes so, and it seems likely that the additional fasting assisted in improving the therapeutic result.

Failure of the treatment due to vomiting was encountered more often among those treated with mepacrine than with male fern—in 5 out of 144 (3.5%) treated with male fern only, but in 6 out of 75 (8%) treated with mepacrine only. The difference is without statistical significance, and probably unimportant except in those suffering from an infection with *T. solium*. Such patients, should they vomit, would almost certainly acquire a heavy infection with cysticerci, for mature segments of the parasite would be brought into the stomach and upper small intestine, where they and their contained eggs would be digested by the intestinal ferments, and the larvae thus liberated would gain entrance to the body proper. It is suggested, therefore, that mepacrine should not be employed in patients suffering from *T. solium* infections.

A further point which is thought to be important is the administration of the anthelmintic in a draught or by duodenal tube rather than in capsules. The head of the worm is usually attached high up the small intestine, and if capsules are administered there is some risk that they may not rupture and liberate their contents until they have passed the head. This risk is aggravated by prolonged storage of capsules whereby they become hard and difficult to dissolve. However, provided the anthelmintic is administered in a draught and the patient fasts for 48 hours before treatment, excellent results may be expected after treatment with either mepacrine or male fern in the dosage regimes here employed. The results certainly appear better than those reported from the use of dichlorophen (2:2′-dihydroxy-5:5′dichlorodiphenylmethane). The best of these so far reported are those of Schneider (1959), who obtained cures in 42 of 61 cases (68.5%), and of Mazzotti and Méndez (1956), who cured 34 of their 49 cases—that is, 69.4%. In other reports the results obtained with this drug have been much inferior to these.

Finally, practitioners with fashionable practices may wish to note that among patients who were recently treated for tapeworms at the hospital there have been three who were fashion models. Three fashion models developing tapeworm infections do not make this an occupational disease any more than three swallows make a summer, but the chain of events leading to the infection appears clear. These women are entertained in fashionable restaurants, probably more often than most, and underdone or rare steak is a fashionable meal. Their infection and the common occurrence of the disease in Great Britain underline the desirability of impressing upon restaurateurs and the restaurant-frequenting public the desirability not only of thoroughly cooking beef but also, so far as underdone beef is concerned, of sacrificing gustatory gratification to intestinal integrity.

Summary

Information on the results of treatment of tapeworm infections under standard conditions is scanty, and observations have therefore been made under such conditions in 240 cases.

No statistically significant difference in results was found between five different treatment regimes, including administration of male fern orally or by duodenal tube and of mepacrine by the same routes.

Factors which may give rise to poor results when these regimes are used include inadequate fasting, administration of male fern in capsules instead of in a draught, and, when doses of anthelmintics of small volume are administered through a duodenal tube, failure to take into account the amount required to fill the tube before any is delivered from its distal extremity.

Unfavourably false impressions of the efficacy of a treatment for tapeworms may be obtained unless patients

are followed up for at least four months in cases in which the head of the worm is not recovered after treatment.

Failure of treatment due to vomiting was encountered more often among those treated with mepacrine than with male fern. As vomiting in patients with *T. solium* infections may give rise to cysticercosis, treatment with mepacrine in such cases is best avoided.

Our thanks are due to Sir Neil Hamilton Fairley, Sir George McRobert, and Dr. J. H. Walters for permitting us access to their case records; to Dr. D. S. Ridley and his staff for laboratory help; and to Professor A. Bradford Hill and Dr. W. J. Martin, of the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

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TOXIC EPIDERMAL NECROLYSIS OCCURRING IN A CHILD

BY

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The term "toxic epidermal necrolysis" was first used by Lyell (1956) to describe a syndrome of toxic origin whereby large areas of epidermolysis preceded peeling, followed by fairly rapid tendency to healing. The skin was extremely tender at the onset. Bullous formation, although common, was only incidental to the process. Lyell had described four cases in adults. Lang and Walker (1956) described a case of an unusual bullous eruption in a Bantu male adult which appears to have been a similar condition, and in 1957 they described four other cases occurring in adults. Rook (1957) added another case to the collection.

So far no cases of this syndrome in children have been reported, although occasional cases are known to have occurred. A case is here reported in a young boy.

Case Report

A boy aged 3 was admitted to hospital with a day's history of blisters, which had been getting progressively bigger and more numerous. Two days previously he had developed what was diagnosed as impetigo. Fourteen days previously he had several attacks of vomiting, which occurred immediately after food and fluids. His small brother, aged 2, had diarrhoea and vomiting at the same time. A diagnosis of cyclical vomiting was made. The vomiting stopped a couple of days later, after "ancoloxin" (pyridoxine hydrochloride and meclozine hydrochloride) had been given.

For the next five days he was anorexic and irritable, after which he felt perfectly fit again. His brother (aged 2) had then been well for some time.

A week before admission another brother, aged 6 years, developed impetigo, and he was given neomycin ointment by his own doctor. Two days prior to admission the patient developed septic spots on his chin, and a diagnosis of impetigo was made. He was also given neomycin ointment. His mother said that he also complained of transient girdle pains, but cursory examination by her revealed nothing. On the day before admission he was noticed to have a few small blisters on the front of his chest. These got bigger and more numerous during the rest of the time at home. The skin also started to peel. The mother applied neomycin ointment to the affected areas. That night he could not lie down, and cried continuously because of the extreme tenderness of the skin.

There was no relevant family or past history.

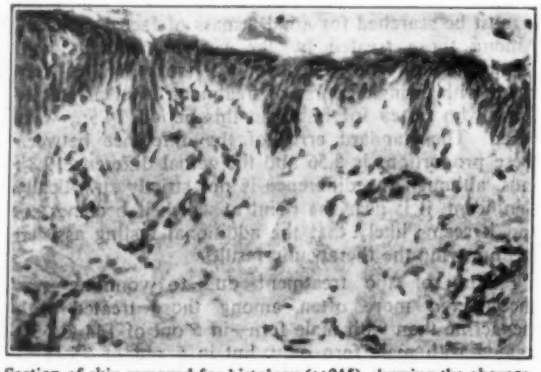
On admission he looked extremely ill, but was not moribund, dehydrated, photophobic, or unconscious. His temperature was 100° F. (37.8° C.), pulse 104, and respirations 25.

Physical examination was difficult because of the tender skin over his trunk and upper parts of the limbs. He had impetigo-like lesions around the mouth and chin. There were large areas of peeled and dead skin on the front and back of the trunk. No blisters were seen, but the mother insisted that they had been present the day before. The underlying dermis was raw, moist, pink, and oozing. Between these areas the skin was erythematous and in places wrinkled. Nikolsky's test was positive. Wrinkling and peeling were also noticed on the forehead and in the right retroauricular region. Areas of erythema were also noticed in the flexures of all limbs. Conjunctivitis was not present. In his mouth there was a membranous tonsillitis. The membrane was a dull white colour and very adherent to the tonsil. There were also tender tonsillar lymph nodes. His abdomen was difficult to examine because of the painful areas on its surface. Despite a thorough search no lesions were found in any other system.

Investigations.—A swab of the skin from the impetiginous areas grew mainly *Streptococcus viridans*; a throat swab also grew the same organism. A tonsillar swab did not grow diphtheritic organisms, Vincent's organisms, *Staphylococcus aureus*, or haemolytic streptococcus. On the day of admission a skin biopsy was performed from an erythematous area on the back. It was noticed that the epidermis tended to slither over the dermis during the incision. The histological report of the tissue stated: "The superficial part of the epidermis in the small fragment of the skin has been shed, including the stratum corneum and most of the stratum granulosum (see illustration). There is moderate inflammatory cell infiltration in the dermis consisting of round cells and neutrophil polymorphonuclear leucocytes. The appearances are consistent with the clinical diagnosis of epidermal necrolysis." Estimation of the herpes-virus-neutralizing bodies on admission was negative. A further estimation two months after he had been discharged from hospital also proved to be negative.

Treatment

As the skin was tender and peeling he was covered all over the trunk with "eucerin" (hydrated ointment of wool alcohols) dressings. It was very painful to remove these coverings for the next few days because of the skin tenderness. In an effort to combat the infection and the membranous tonsillitis, he was given oral chloramphenicol palmitate suspension, 250 mg. initially and 125 mg. six-hourly thereafter for six days.



Section of skin removed for histology (×215), showing the absence of the stratum corneum, and most of the stratum granulosum.

In view of the previous cases and the fear that the lesion would progress further and cause a collapse, oral cortisone was given, starting with 50 mg. on the first evening, followed by 25 mg. six-hourly the next day. The drug was continued for the next 10 days in gradually diminishing doses.

On the day after starting treatment several new areas of peeling had occurred. This was to be expected, as they arose from the erythematous wrinkling area of the previous day. This was also noticed around the eyes. He was given prophylactic "neo-cortef" eye drops.

On the following day his impetiginous lesions had gone, the throat was clean, and he said that he felt a good deal better. Although his skin condition was still painful he was more tolerant of examination. His temperature had fallen to normal.

His improvement was maintained; the tenderness of the skin disappeared two days later and there were no new areas of peeling, although the epidermis in the old areas continued to come away. A new epidermis grew in these regions without any evidence of scarring or depigmentation.

He was discharged from hospital 12 days after admission.

Comment

This syndrome is well defined, so that the diagnosis is fairly suggestive. Conditions such as dermatitis herpetiformis, pemphigus, pemphigoid, Stevens–Johnson syndrome, and erythema multiforme are usually well differentiated on clinical and histological grounds. If it be claimed to be a drug eruption in all the reported cases, there seems to be nothing common at all in the medicaments taken before the onset of the illness. In the above case the only drugs known to have been used were pyridoxine hydrochloride and meclozine hydrochloride by mouth, plus local neomycin ointment.

In the South African cases the Bantu man had taken (for roundworm infestation) oil of chenopodium, which is known to be toxic to the liver but not to the skin, and local methyl salicylate plus capsicum, as a counter-irritant for lumbar backache. It was interesting to note that the erythema and vesiculation did not occur over these locally treated areas. Two other South African cases had phenolphthalein as an aperient before the epidermolysis occurred. In other cases recorded by Lang and Walker (1956) and by Lyell (1956) drugs such as penicillin, Dover's powder, aspirin, and phenylbutazone had been taken. Three other cases gave no history of having taken drugs (Lang and Walker, 1956; Lyell, 1956; Rook, 1957).

The nature of the toxin has yet to be discovered. The toxaemia must be responsible for the prodromal symptoms. In Rook's case there was a sore throat with vomiting the day before onset; other symptoms being diarrhoea for one day, low backache for a week (Lang and Walker), sore throat (Lang and Walker; Lyell), and pain in left groin for some hours only (Lyell). In the above case the boy had bilateral girdle pains on the night before the appearance of the blisters. The history of vomiting 14 days before blistering could be explained either as a premonitory symptom or as an attack of cyclical vomiting, similar to that of his brother aged 2. As in the adult cases, the eruption reached its greatest extent in 24 hours.

Corticosteroids have been tried in several cases (Lang and Walker, 1956, 1957; Lyell, 1956), including the above case. The part they play is difficult to evaluate, and whether they shorten the course of the illness is unknown. If this is an immunity reaction the corticosteroids will certainly interfere with the process. They should be used at least in severe cases, as the reports suggest. It was probably wise to use the drug in the above case as the child had gone downhill so quickly, and seeing him now fit makes one realize how ill he was on admission. As in the other cases, antibiotic therapy was advisable to combat any toxaemia due to infection.

The histology in the present case, as in the others, shows the epidermis as the target for the toxic onslaught. This is the essential abnormality with epidermal necrolysis. The nearest resemblance to this condition is scalding of the skin (Lyell, 1956; Rook, 1957). There are slight differences in the depth of the epidermal necrosis. Lang and Walker claim epidermal-dermal cleavage in their cases which went to histology, the bullae having been formed in this plane. Lyell described a similar change in one of his cases. In the above case the cleavage was intra-epidermal, as described in reports of one other of Lyell's cases and one of Rook's. There were inconspicuous inflammatory changes in the corium, as in the other cases. The resemblance of the skin condition to scalding suggests that its recognition may have an important bearing in forensic medicine.

Summary

This is believed to be the first description of toxic epidermal necrolysis in a child, a boy aged 3. There were premonitory symptoms of toxaemia followed by tenderness of the skin, which loosened and later peeled. Recovery was complete. It is thought that the syndrome is due to a toxaemia of unknown origin, and no other common factor linking other cases can be suggested. The use of antibiotics and corticosteroids is recommended.

I thank Dr. F. J. S. Bowman, family doctor, for permission to report this condition in one of his patients, and Dr. A. Lyell for his helpful advice and constructive criticism.

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FOOD OBSTRUCTION OF THE SMALL INTESTINE

A REVIEW OF 15 CASES

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Obstruction of the small intestine by food has been described on many occasions. Some predisposing factors and numerous causative foodstuffs have been reported. Fifteen cases are reviewed, with special reference to the aetiological factors found and the modes of treatment adopted.

Obturation of the bowel is an important consideration when a case of intestinal obstruction is clinically assessed. Uppermost in the mind of the surgeon is the bizarre clinical picture which may result from the halting passage of a gall-stone through the intestine. In addition to food boluses and gall-stones, other possible causes of obturation include intestinal parasites, faecaliths,

enteroliths, concretions, bezoars, foreign bodies, and meconium in the newborn (Storck, Rothschild, and Ochsner, 1939).

In the case of food boluses, although instances of impaction have been reported throughout the alimentary tract, by far the commonest site has been the small bowel. In all of our cases impaction has occurred in this region. It is becoming evident that, as the number of reports increase, more complete recognition may be given to the condition, which in some cases is capable of diagnosis before treatment. It is further submitted that in dealing with the condition several courses of action, involving little risk to the patient, may be clearly advised.

The main features of a series of cases are shown in the Table. These represent the total occurring during a four-year period in two general hospitals, and most of them were personally observed and treated. Taking into account all types of intestinal obstruction admitted, but excluding strangulated external herniae, food boluses were the cause in 4%. All the patients made uneventful recoveries apart from Case 13, in which wound infection prolonged the stay in hospital.

Clinical Features

Various aspects have previously been described by Elliot (1932), Storck *et al.* (1939), and Ward-McQuaid (1950). Many other authors have recorded specific points of interest.

Sex and Age.—No particular sex or age incidence was noted. Males and females were more or less equally affected, the age range being from 7 to 71. There seemed to be a greater incidence in the fourth and fifth decades, and this concurred with the finding of Elliot in his review of 39 collected cases.

Symptoms.—All the patients had abdominal colic, and often it was severe. There was associated vomiting, and, while in most cases bowel action had been normal, two complained of severe diarrhoea. The symptoms were of rapid onset, with a short duration before arrival in hospital. In nine patients admission was within 12 hours, and in no case was it longer than 36 hours, from the onset of symptoms.

Signs.—These tended to present in two groups: (1) those having abdominal distension with visible peristalsis, palpable coils of bowel, and increased bowel sounds—indicative of typical small-bowel obstruction, and (2) those having abdominal tenderness and guarding, more often localized to the right and thus giving rise to a pre-operative diagnosis of acute appendicitis. In the second group distension of a minor degree was often noted, as was associated increase in bowel sounds. However, since the predominant signs were tenderness and guarding in the right iliac fossa, the diagnosis of acute appendicitis was preferred.

Site of Obstruction.—Impaction of the bolus at all levels from the upper jejunum to the ileo-caecal valve has been described, and in some instances multiple boluses have been found. This was exemplified in the present series, though impaction in the ileum was commonest. Furthermore, it usually occurred in the lower ileum, but in no case at the ileo-caecal valve. A noteworthy point was the firmness of the impaction. So much was this so in Cases 6 and 9 that necrosis of the wall of the bowel had occurred. Indeed, in Case 6 perforation of the proximal ileum had been produced, with peritonitis.

Previous Attacks.—In four of the cases there were reasonable grounds to suppose that a previous attack, not amounting to frank obstruction, had occurred. It is known that in Case 9 the offending foodstuff, parts of a lemon, had been eaten two months before, and in the period prior to admission the patient had suffered frequent attacks of colic and distension. Temporary self-resolving obstruction is probably a common occurrence, and is dismissed by patient or doctor as being a simple stomach upset. It is likely that in only a very small proportion does impaction with overt small-bowel obstruction occur.

Subsequent Attacks.—One patient (Case 3) was readmitted to hospital two years later with similar though less marked symptoms and signs. She confessed to having swallowed a whole small onion in spite of advice given regarding the importance of proper mastication of food. The attack resolved rapidly after admission, and operation was not thought to be necessary. In this case the previous history influenced the decision to adopt a " wait and see " policy.

In a follow-up, 13 out of the 15 cases were traced. Apart from Case 3, no patient had had a further attack. In most of these a period of from two to five years had elapsed since operation.

Aetiology

Type of Food.—Ward-McQuaid (1950), in a review of the accumulated literature, cites 45 different foodstuffs causing obstruction in 178 patients. Since this time many more foods have been added to the list by other writers. Foods largely consisting of fibre or pith, surrounded by indigestible skins, feature prominently. In our series the main culprit has been the orange (nine cases). This fruit, or rather the internal supporting pithy part of it, has often been reported as the cause of obstruction in this country (Latchmore, 1940 ; Jones and Davies, 1945 ; Radclyffe, 1945 ; Aird, 1949). Geographical location and the social conditions prevailing may influence the type of foodstuff available. In the U.S.A., obstruction due to the persimmon seems most common (Newburger, 1941). In Argentina, according to Delrio, Paz, and Carpanelli (1944), oranges and peaches have been incriminated. In the first world war, when famine was rife in Germany and Russia, a number of cases occurred due to conglomeration of ingested oat husks. Thirty-six cases of this nature were reported by Tigi (1922).

Eating Habits.—In the otherwise normal person with a full set of teeth, mere inadequate mastication may be the only contributory factor. This can occur as the result of hurry, accident, drunkenness, or even politeness. In children, food may be bolted without thought of chewing.

Teeth.—Absent or poor natural teeth and ill-fitting dentures will be found to be a factor in most cases. This was evident in all the adult cases where the state of the teeth was known. In some there were a few natural teeth which had little function in mincing food into smaller particles. This was also apparent when complete or incomplete inefficient dentures were worn. A poor fit or a lack of comfort when eating prompted patients to remove them. As a result compressed rather than fragmented food was swallowed. In both of the

cases occurring in children, dentition was normal and bolting was probably the major fault.

Previous Operations.—Operations on the stomach which permitted food to leave the organ more quickly than usual had been performed in five cases. It is suggested that such food, not having been subjected to the normal gastric juices and milling effect in the stomach, passes rapidly into the small intestine, swelling *en route* and later impacting. Four of these patients (Cases 1, 2, 4, and 5) had had a full-width Polya-type reconstruction after partial gastrectomy for duodenal ulcer. Norberg (1955, 1956a, 1956b) has the largest reported experience of this type (15 cases). There have been other accounts by Baumeister and Darling (1947) and Rowling (1956). From our own observations, bolus obstruction is commoner after gastrectomy than the various types of "loop" obstruction as described by Stammers (1952, 1954). The remaining patient of the five (Case 8) had obstruction after a gastro-jejunostomy performed 17 years previously. Orange pith was responsible, as in the only other case we have been able to trace in the literature (Delrio, *et al.*, 1944).

Segments of tomato skin found causing obstruction in Case 6.

Other Intra-abdominal Lesions.—Diverticula can be sites of accumulation of food debris. In Case 6, with obstruction of the ileum by tomato skins, duodenal and jejunal diverticula were present. It is reasonable to assume that the skins accumulated in one or more of the diverticula, as a later barium-meal examination demonstrated a bolus in a duodenal diverticulum. In this case there were 40 segments of skin, each rolled up and glued together to form a "faggot" (see illustration). A similar state of affairs, in which food was retained in intestinal diverticula, has been described by Wangensteen (1955). In Cases 14 and 15, a Meckel diverticulum was present. The diverticulum and the adjacent ileum were packed full of coconut and apple-pulp respectively, causing complete small-bowel obstruction. Lodgment of a food bolus at the site of a stricture in the small bowel has precipitated complete obstruction. Krecke (1929) has described this occurrence at the site of an entero-anastomosis, and Krukenberg (1930) similarly reported obstruction at the site of a tuberculous stricture. There must have been many other instances.

Treatment

By the time many of these cases reach hospital minor degrees of temporary bolus obstruction are likely to have been overcome and no specific treatment will be called for. Evacuation of the large bowel should be promoted by suppository or enema.

In other instances the pre-operative diagnosis, as has already been suggested, will have been acute appendicitis or small-bowel obstruction of doubtful aetiology. In these, either a right "gridiron" or paramedian incision will have been performed. Gastric suction and intravenous fluids may have been started as routine measures, although dehydration and electrolyte upset is not a prominent clinical finding.

On locating a bolus as the cause of obstruction, its character can often be identified through the stretched bowel wall. It is recommended that the more desirable procedure in these circumstances should be fragmentation of the bolus by gentle manipulation and the pieces "milked" into the caecum and ascending colon. Here they may be further broken up, if necessary, to prevent possible enterolith formation and subsequent colonic obstruction. This was performed in 10 cases without harm to the bowel wall or delay in the return of gut movements.

If the "closed" fragmentation and "milking on" technique is not possible—for example, where the bolus is too hard (Case 13), too firmly impacted (Case 6), or impacted at a high level (Case 2)—enterotomy should be carried out. This may have to be done directly on to the bolus, as dislocation proximally may cause further damage to the bowel.

In all cases, when the primary site of obstruction has been located a search of the rest of the small bowel should be undertaken to exclude the presence of other boluses. This is of particular importance if enterotomy is contemplated, as all may then be removed through a suitably placed incision. If a perforation is present, it can be incorporated into the enterotomy incision or closed separately by simple suture, depending on the site of the perforation. Enterotomy introduces the factor of infection and has caused wound sepsis, with prolongation of stay in hospital (Case 13). Use of prophylactic antibiotics is a matter for personal choice. In no instance was the peritoneal cavity drained.

If a Meckel's diverticulum is found it can be simply excised after moving the bolus into the caecum. In Case 14, however, where there was considerable distension of the bowel and the diverticulum was short and wide-necked, it was considered safer to pass the bolus into the caecum and then leave well alone.

Conclusions

In reviewing all the aspects of the foregoing cases one salient fact has emerged. Provided food is adequately chewed, it is very unlikely that any one of the other factors noted will cause obstruction by food bolus.

Poor dentition led to inadequate mastication in 11 out of 12 adult patients. Therefore it is important that proper advice should be given regarding teeth, eating habits, and food, especially after partial gastrectomy and gastro-jejunostomy. The patient should know that failure to possess or use efficiently functioning dentures may be dangerous.

It is evident that the pithy residue of citrus fruits is particularly apt to become impacted. Orange and lemon pith was identified in 10 out of 15 cases. Therefore a person incapable of proper mastication should be advised to avoid these and similar fruits.

Details of Cases

Case No.	Sex and Age	Symptoms	Duration in Hours	Physical Signs	Predisposing Factors		Nature and Site of Food Bolus	Operative Treatment	Previous Attacks
					Intra-abdominal	Teeth			
1	M 39	Colic and vomiting	12	Abdominal distension. Increased bowel sounds	Polya gastrectomy 2 years before	Natural lower incisors and upper molars. Upper denture often not worn	Orange pith. Upper ileum	Fragmentation. Milked into colon	Nil
2	M 64	Severe colic and vomiting	4	General tenderness. Bowel sounds +++	Polya gastrectomy 8 years before	Upper and lower dentures	Orange pith. Upper jejunum	Enterotomy	,,
3	F 44	Colic and vomiting	24	Distension. Visible peristalsis	Nil	A few poor natural teeth	? Orange pith. Upper ileum	Milked into colon	,,
4	F 49	,, ,,	6	,, ,,	Polya gastrectomy 6 years before	Wearing upper and lower dentures	Orange pith, eaten day before. Lower ileum	Fragmented. Milked into colon	,,
5	F 63	,, ,,	8	General tenderness. Visible peristalsis	,, ,,	Not known	Orange pith. Upper ileum	,, ,,	,,
6	F 61	,, ,,	10	Distension. Visible peristalsis. Bowel sounds +++	Duodenal and jejunal diverticula	False teeth, but not wearing them	Tomato skins. Eaten week before. Mid-ileum; perforation in upper ileum	Enterotomy. Closure of perforation	3 years previously
7	F 54	,, ,,	36	,, ,,	Nil	Not known	Orange pith. Upper ileum	Milked into colon	1 year previously
8	F 39	,, ,,	12	Tenderness. Bowel sounds +++	Gastro-jejunostomy 17 years before	Wearing false teeth (part plate)	Orange pith, eaten day before. Ileum	,, ,,	Nil
9	M 54	,, ,,	7	Tenderness. Some distension. Bowel sounds infrequent	Nil	Wearing false teeth	Half a lemon with rind in lower ileum. Bits of rest of lemon above. Near perforation	Enterotomy	Attacks of colic and distension for two months before admission
10	F 71	,, ,,	24	Tenderness and distension. Bowel sounds infrequent	,,	No teeth of any description	Orange pith, eaten week before. Lower ileum	Milked into colon	Nil
11	M 53	,, ,,	12	Tenderness in upper abdomen	,,	False	Orange pith. Upper ileum	,, ,,	Probably two; 5 years before
12	M 68	Colic, vomiting, and diarrhoea		Tenderness in R.I.F. Abdominal distension	,,	Wearing false teeth	Hard bolus of doubtful nature. Lower ileum	Crushed and milked into colon	Nil
13	F 63	,, ,,		Tenderness in R.I.F.	,,	False; top set only	Nuts from nut chocolate eaten 2 days before. Lower ileum	Enterotomy	,,
14	M 10	Colic and vomiting	24	Tenderness in right abdomen. Distension. Bowel sounds +++	Meckel divertic.	Good	Coconut in lower ileum and diverticulum	Milked into colon	,,
15	M 7	,, ,,	12	Tenderness and guarding in R.I.F.	,, ,,	,,	Apple pulp and skin at site of diverticulum	Meckel divert. resected and bolus removed	,,

Diagnosis in cases presenting as small-bowel obstruction of doubtful cause will rest on detailed inquiry into the patient's previous history and a correlation of this with the symptoms and physical signs. Particular note should be made of the subject's dietary and eating habits, ability to chew, previous operations, and other known intra-abdominal conditions. A pre-operative diagnosis will thereby become possible in some cases. Treatment should be prompt and as outlined. Serious complications such as perforation, peritonitis, or even death from simple obstruction may otherwise occur. Some of the earlier cases described were found at post-mortem examination, and in 1954 an unsuspected fatal case was noted in the *British Medical Journal*.

Finally, Case 2 is related in greater detail. The events which took place are of particular interest, and serve to re-emphasize many of the points already discussed.

This patient was a theatre night porter in our own hospital, and had had a partial gastrectomy eight years before. During an emergency operating session, between transporting cases to and from the wards, he was given a portion of orange to eat by a nurse. He admits that he ate and swallowed it hurriedly, and did not have his teeth in at the time. Symptoms followed the next day, and he reached the operating table in his own theatre that night. The undigested orange pith was recovered by enterotomy from the jejunum.

Summary

Fifteen cases of food bolus obstruction of the small bowel have been described, with their method of treatment by operation without mortality.

Aetiological factors have been outlined and ways of management suggested.

We thank Mr. D. B. E. Foster, Mr. J. S. H. Wade, Mr. H. O. Jones, and Mr. D. H. Jenkins, of Llandough Hospital, and Mr. Evan G. Griffiths, of Bridgend General Hospital, for permitting us to publish details of the cases reviewed; Professor Lambert C. Rogers for his helpful advice; and Mr. L. T. S. Williams, of the photographic department, Llandough Hospital, for his help in preparing the illustration.

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ORANGE-PITH ILEUS AFTER PARTIAL GASTRECTOMY

BY

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During the past decade it has become increasingly apparent that after the Polya type of gastric resection there is a very real risk of subsequent intestinal obstruction by the impaction of foodstuffs in the small bowel. The present paper is prompted by the recent occurrence on one surgical unit of three such cases, in all of which orange-pith was the offending substance. This particular complication of gastrectomy should be a preventable cause of morbidity, and it is therefore worthy of wide recognition.

Case 1

The patient, a man aged 63, was admitted to hospital on October 10, 1956. In June, 1955, a retrocolic Polya gastrectomy had been performed for chronic duodenal ulcer, and he had subsequently been perfectly well until one day before the present admission. He then awoke in the morning with severe central abdominal pain, colicky in nature, each spasm lasting about one minute and recurring every few minutes. Twelve hours after the onset vomiting began, and he vomited in all about ten times. He had no bowel action and passed very little flatus after the onset of the pain, which continued intermittently up to the time of his admission.

On examination he looked ill and was slightly dehydrated. His temperature was 97.6° F. (36.4° C.), pulse 90, and B.P. 170/90. The abdomen was moderately distended, but showed no localized tenderness or guarding. Bowel sounds were normal. There was an incisional hernia through part of the gastrectomy incision. Nothing else of significance was found. A straight radiograph of the abdomen showed distended loops of small bowel and fluid levels, thus supporting the clinical diagnosis of acute intestinal obstruction. Laparotomy was advised.

The abdomen was opened through the previous scar, and numerous adhesions required division. The upper part of the small intestine was distended, and on following it down it was found to be obstructed by a mass some 4 by 1½ in. (10 by 3.8 cm.) which was firmly impacted in the lumen at a point about 4 ft. (122 cm.) proximal to the ileo-caecal valve. The "mass" was removed by enterotomy, and found to be composed of four tightly compressed and undigested pieces of orange, inclusive of peel. After closure of the incision in the bowel, the operation was completed by repair of the incisional hernia. His post-operative course was uneventful save for the development of a wound infection.

Case 2

A Hungarian aged 49 was admitted to hospital on June 2, 1958. His history was difficult to obtain, as he spoke little English, but it appeared that he had had intermittent colicky central abdominal pain for about 24 hours. He had vomited four times and there had been no bowel action since the pain began. A gastric operation had been performed in Hungary two years previously.

On examination he was in good general condition, though having fairly severe spasmodic pain. His temperature was 98° F. (36.7° C.), and pulse 70. The abdomen was not distended and was soft on palpation except during the bouts of colic. A straight radiograph of the abdomen showed several distended coils of small bowel with some fluid levels, and there was very little gas in the large bowel. Acute intestinal obstruction was diagnosed. At operation the same day obstruction was found at about the middle of the small bowel, due to a tightly impacted indentable mass. This was removed by enterotomy and found to be composed of several large pieces of orange-pith firmly compressed together. Exploration of the upper abdomen was difficult on account of adhesions from his previous operation, but it appeared that a Polya-type partial gastrectomy had been performed. His post-operative course was uneventful.

Case 3

A man aged 56 was admitted to hospital on December 3, 1958, with a 12-hour history of intermittent colicky upper abdominal pain. This had begun suddenly, was severe for the first few hours, and then diminished somewhat in intensity. There had been some nausea, but no vomiting. He had passed no flatus since the onset of the pain. In 1947 he had undergone a Polya-type partial gastrectomy for chronic duodenal ulcer and had subsequently remained well until the onset of the present episode.

On examination he looked ill. His temperature was 98° F. (36.7° C.), and pulse 80. The abdomen showed slight distension and was tender in its upper part; there was no guarding or rigidity. Bowel sounds were increased. A straight radiograph of the abdomen showed two distended loops of small bowel with fluid levels.

A diagnosis of subacute intestinal obstruction was made, and as his symptoms appeared to be improving somewhat he was treated in the first instance by gastric aspiration and intravenous fluids. For the first 12 hours on this regime his pain diminished, but bouts of severe intestinal colic then recurred, and laparotomy was advised. On opening the abdomen distended small bowel presented, and on following the distended coils downwards an elongated indentable mass was found, firmly impacted at a point about 2 ft. (60 cm.) proximal to the ileo-caecal valve. The impacted mass was readily removed by enterotomy. It consisted of several large pieces of orange-pith compressed to form a mass 3 by 1½ in. (7.5 by 3.8 cm.). On subsequent questioning, the patient recalled that he had hurriedly eaten an orange about 12 hours before the onset of his symptoms. His post-operative course was uneventful.

Discussion

Intestinal obstruction by foodstuffs was well reviewed by Ward-McQuaid (1950). He traced 178 reported cases, and four of these patients had previously undergone a Polya-type partial gastrectomy, whilst a further case followed gastro-enterostomy. In four out of this group of five cases the obstructing agent was orange-pith. Since 1950 numerous cases of foodstuff ileus following Polya gastrectomy have been reported: Stalker and Gotham (1950), obstruction by orange-pith; Pecora, Pepe, and Cooper (1952), obstruction by macaroni; Rowling (1956), two cases of obstruction by undigested orange; MacPhee (1956), obstruction by orange bolus; Ward-McQuaid (1956), obstruction by orange bolus; Rains, Dawson-Edwards and Brookes (1956), obstruction by coconut; Ryan (1956), obstruction by orange bolus; Norberg (1955), seven cases of foodstuff obstruction, in five of which citrus fruits were involved; Norberg (1956), eight cases of obstruction by orange bolus; Davies (1956), obstruction by orange bolus; MacCarthy (1956), obstruction by orange bolus. The three cases reported above bring the total number of recorded cases of post-gastrectomy obstruction by food to 33, and the obstruction was caused by citrus fruits, particularly oranges, in no fewer than 28 (84%).

There is thus no room for doubt that this complication is a very real hazard to the patient after Polya gastrectomy. So far as I am aware it has been reported only once following the Billroth I operation (Norberg, 1956), probably because it is rarely possible to make a gastro-duodenal anastomosis which is appreciably wider than the lumen of the narrowest part of the small bowel.

Although disimpaction of the obstruction has necessitated enterotomy in the majority of the reported

cases, the mortality has been low, though, as in other forms of intestinal obstruction, delay in treatment may lead to death, as in the case described by Davies (1956).

Intestinal obstruction by foodstuffs would seem to be common enough to warrant the strong recommendation that all patients who have undergone partial gastrectomy or gastro-jejunostomy should subsequently be given careful advice regarding their diet. Oranges constitute the most important hazard, so that only their juice should be taken. All bulky, fibrous, and coarse articles of diet should be thoroughly masticated or chopped up before ingestion. The provision of a small stoma could be used as an additional safeguard in individuals who are considered likely to ignore or forget such advice, but if patients are made aware of the particular danger to which their operation exposes them, most of them should have little difficulty in avoiding this complication.

Summary

Three cases are reported of intestinal obstruction by orange pith after partial gastrectomy. Recent case reports indicate that this complication has become relatively common. The importance of dietary advice to patients after gastrectomy is stressed.

My thanks are due to Mr. E. Stanley Lee for permission to publish the case reports and to Mr. W. H. W. Jayne, who performed the operation on the first patient.

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Medical Memoranda

Thyroid Carcinoma After Irradiation in Adult Life

Considerable interest has been aroused during the past decade regarding the carcinogenic effects of irradiation on the thyroid gland.

Wilson *et al.* (1958) reviewed the literature and reported the development of thyroid neoplasms in nine patients who several years previously had received ionizing irradiation. Seven of the cases were proved carcinomata and two were adenomata with a malignant predilection. In one of the malignant cases the irradiation was given during adult life.

Goolden (1958) related a similar development of thyroid carcinoma in three cases, two having received the *x*-ray therapy in adult life. He remarked on the paucity of reported cases of thyroid carcinoma after irradiation to the neck region in adult life and stressed the importance of reporting these cases.

Since 1935, 104 cases of carcinoma of the thyroid have been diagnosed in this department by the histological examination of surgical material. Sixty-three of these patients have been interrogated, either personally or indirectly with the co-operation of the consultants and the general practitioners by questionary, for a history of exposure of the thyroid gland to irradiation. Attempts to trace the remaining 41 have so far been unrewarding. In 4 of the 63 cases interrogated an affirmative answer has been received, but in one, that of a woman aged 35, the irradiation was administered to the thyroid only five years before the diagnosis of a malignant adenoma was made. The interval was thought too short for irradiation to have had any significant carcinogenic effect, and the case is not reported.

The other three cases are reported here. Unfortunately there is no record of the dose of irradiation, but it was sufficient to alleviate the condition and was probably greater than 2,000 r, as pointed out by Wilson *et al.* (1958).

CASE REPORTS

Case 1.—A woman aged 79, who had had *x*-ray therapy in 1940 for thyrotoxicosis at the age of 63, was admitted to hospital in January, 1956, with a fixed, smooth, firm, and greatly enlarged right lobe of the thyroid gland. Partial removal of a tumour involving the whole of the right lobe and infiltrating into the trachea was carried out, followed by radiotherapy. The left lobe was smooth; it was regarded as normal, and was left *in situ*. Histological examination revealed an anaplastic carcinoma. The latent interval between the time of irradiation and diagnosis was 16 years. The patient died six months later.

Case 2.—A woman aged 59, who had had *x*-ray therapy in 1926 for thyrotoxicosis at the age of 29, was seen in April, 1956, and found to have a very firm and tender right lobe of the thyroid associated with hard palpable glands in the right posterior triangle of the neck and the right axilla. Subsequently, the removal of a malignant mass involving the isthmus and the right lobe of the thyroid, infiltrating along the right jugular vein and upper mediastinum, was carried out, followed by radiotherapy. Histological examination revealed an anaplastic carcinoma. The latent interval was 30 years. The patient died three months later.

Case 3.—A woman aged 46, who had had *x*-ray therapy in 1937 for thyrotoxicosis at the age of 26, was admitted to hospital in July, 1957, in congestive heart failure complicating thyrotoxicosis, which settled down with carbimazole and digoxin therapy. Partial thyroidectomy was carried out in February, 1958. Examination revealed a papillary adenocarcinoma in a diffusely enlarged thyroid gland. The latent interval was 21 years and at the time of writing the patient was still well with no signs of recurrence.

COMMENT

It is seen that less than 5% of the 63 patients in whom it has been possible to obtain information gave a history of previous irradiation with a latent period of sufficient length for the irradiation to have had any carcinogenic effect on the thyroid gland. They were all female patients, in whom there is a high incidence of spontaneously occurring carcinomata of the thyroid. In this series, 88 were females and 16 males. Again, the histological types were those which occurred most frequently in the age groups to which these patients belong, so that the finding may well be fortuitous. Nevertheless, the cases seem worth reporting.

I thank Professor J. H. Biggart for his help. I am indebted to Mr. J. W. S. Irwin, Mr. E. W. McMechan, and Mr. E. Morrison for permission to publish the cases.

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Reviews

ARMY PSYCHIATRY IN THE WAR

Psychiatry in the British Army in the Second World War. By Robert H. Ahrenfeldt. Foreword by J. R. Rees. (Pp. 312 +xv. 35s.) London: Routledge and Kegan Paul. 1958.

As the content of medicine enlarged and as the total size of the Army increased to meet the changing pattern of warring, the magnitude of the contributions made by the Army Medical Services to the prosecution of war grew progressively larger. In the second world war there was a planned, systematic distribution of the nation's man-power among industry, the essential civilian services and organizations, and the armed Forces. The Army's quota was insufficient to meet its needs, and towards the end of the war it became necessary to disband a number of its formations, and to reduce the size of others for the reason that the inevitable wastage could not be made good. Into the Army were drafted considerable numbers of individuals who, on account of the poverty of their personal attributes or of their occupational incompetence, were regarded as unsuitable for employment in the Navy or Air Force. Thus it came about that in the Army the overriding need to conserve man-power and to make the very best use of the human material drafted into it profoundly affected every aspect of the conduct of the war. The recruits it received differed markedly among themselves in such attributes as character, temperament, attitudes, biological and social maturity, educability, and educational standard, and acquired skills. Within the Army the tasks to be undertaken by the many very different occupational categories—such as the sapper, the member of a tank crew, the nursing orderly, the infantryman—differed equally markedly and for their efficient performance demanded different constellations of skills, aptitudes, and temperaments. Out of this greatly varying material expeditionary forces remarkable for the occupational diversity of their component units had to be fashioned and trained.

To the Army Medical Services the Army turned for the provision of the means whereby man-power wastage due to preventable disease and avoidable injury might be reduced to the irreducible minimum. To these Services, in association with the Directorate of Selection of Personnel, the Army looked for the prevention of wastage due to disharmony between the individual soldier and the occupational tasks he was required to perform. The prime responsibility of the Army Medical Directorate was that of shaping and directing a mechanism that would ensure that all available knowledge and skill relating to disease prevention, health promotion, and health restoration was applied to the full. To make such application possible the existing branches and directorates within the Army Medical Department were developed and expanded. Others, that were not required in peacetime, were added to them, among them the branch that bore the number A.M.D.11 and which housed the Directorate of Army Psychiatry.

Those who during the war years were in a position to follow the activities of this directorate and of its representatives in the different commands and theatres —the Army Psychiatric Service—could not but be greatly impressed by the great saving of man-power that was effected through the application of expert psychological knowledge, with understanding, to the problems of an army at war. The members of this service were fortunate in many ways. They commanded the support of Sir Ronald Adam, the Adjutant-General, and of Sir Alexander Hood, the Director-General of the Army Medical Services. Than J. R. Rees and G. W. B. James there could not have been wiser or more suitable consultants. The choice of Brigadier H. A. Sandiford as the first director of the service was a very happy one. The young men who gathered around these were quite outstanding in respect of their intellectual equipment, their professional competence, and their ability to adjust themselves to the conditions and circumstances of an entirely novel world. They were unfortunate in that they had to contend with considerable opposition born of misunderstanding and prejudice. Their knowledge of the mainsprings of human behaviour tended to set them apart from the rest of mankind, and commonly they were regarded with suspicion. They came to be called "trick-cyclists," a pejorative term used by some to convey their amused contempt and by others to express their frank and somewhat venomous hostility. Some of the opposition came from the topmost levels of the military hierarchy; some came from their colleagues in the other branches of medicine. Had the advocacy of the senior members of this service not been so skilful, so diplomatic, and withal so convincing, and had the urgency of the need for the control of man-power wastage not been so great, it is possible that the psychiatrists would have been denied the opportunity to serve, to prove their worth, and to demonstrate the great value of the contributions that psychiatry could make to military medicine. However, the opposition to the development of this service was overcome; psychiatry was enabled to make its notable contributions to the war effort, and, because the unique opportunities provided by the circumstances of war were grasped and exploited by the psychiatrists in the field, psychiatry itself underwent a swift development.

So it is that Dr. Ahrenfeldt has a grand story to tell. He tells it exceptionally well. It is a revised and abridged version of a history of the Directorate of Army Psychiatry during the war years that was compiled by the author, mainly in 1948, when he was serving as Deputy Director of Army Psychiatry, and is based upon the official documents in that directorate. The book traces the development of the Army Psychiatric Service from its beginnings in the first world war to the end of the second. It presents authoritative accounts of the work undertaken by the Army psychiatrists in connexion with the selection and efficient utilization of personnel, with disciplinary problems, with morale, training, the treatment of psychiatric casualties in the forward areas, the rehabilitation of ex-Servicemen and repatriated prisoners-of-war, and the disposal of the mentally defective and dull. Most of the factual information contained in this book is to be found scattered through the many volumes of the official (Army) medical history. Dr. Ahrenfeldt is mistaken in thinking that in this history psychiatry claims only some 25 pages altogether; this is the allotment given in one of the volumes. But the value of this unofficial history derives from the fact that it is written by a psychiatrist who served in the directorate and who is competent to form a reasonable judgment concerning the permanent worth of the work that was done. He shows how there emerged out of the

experience gained a clearer appreciation of the importance of the preventive approach and of preventive action in the field of psychological medicine. Now that an interest in mental health occupies the centre of the parliamentary stage it would be well if this book were studied by all concerned. There is much in it that could be considered, with advantage, in discussions concerning the mental health of a population such as ours in days such as these.

F. A. E. CREW.

A MODERN CHINESE PHYSICIAN

Plague Fighter. The Autobiography of a Modern Chinese Physician. By Wu Lien-Teh, M.A., M.D.(Cantab.), Mast.P.H. (Johns Hopkins), Litt.D.(Peking), Sc.D.(St. Johns, Shanghai), LL.D.(Hong Kong). (Pp. 667+x; illustrated. 30s.) Cambridge: W. Heffer and Sons Ltd. 1959.

Those who have leisure to read this very large autobiography will be well rewarded. Dr. Wu, apart from being a very skilled bacteriologist and physician, has the gift of writing impeccable English. His experience of pneumonic plague, which swept through China in the early part of this century, gives a fine picture of the meticulous investigations carried out by him and his staff. The autobiography is, to say the least of it, discursive, but if one can skip long lists of names and get down to the real substance of the text one cannot but be impressed by the skill and energy of this remarkable man. It is often salutary to see ourselves through other eyes. The chapter on missionary work in China gives the considered opinion of a very well read and brilliant observer. Many of those earnest people of the numerous divisions of the Christian faith who gave their whole life, and in many cases their lives, to preaching the Western faith would not be flattered by some of the references to the effect of their work.

The book is more than a mere autobiography; it is a history of China and the Chinese, compiled by a man who, though born in Malaya, is a true "Chinaman," and, as befits his background, he writes from the point of view of a doctor. The chapter on Malaya and her problems is well worth a close study. Dr. Wu's efforts to control the "narcotic" menace is an edifying story. Again, it is doubtful if Great Britain, in spite of her protestations, was in the early stages as helpful as she might have been in dealing with this international problem. Indigenous medicine in China and Malaya is dealt with in a most interesting manner. Dr. Wu has some shrewd and pointed references to our National Health Service, whilst one quotation from an ancient Chinese proverb is peculiarly apt to-day: "The value of drugs does not depend on their price, but upon their effect; the value of prescriptions does not depend on their numbers, but upon their merit."

This autobiography, written by a "son" of Cambridge and St. Mary's Hospital, is a fine record of the individual attainments in medicine of a man who has deservedly gained a high reputation as a scientist, and in addition provides much useful information of the complexities of life in the Chinese nation.

J. C. A. DOWSE.

The third annual *Indian Year-Book of Ophthalmology*, edited by Dr. Vaman D. Sathaye, provides a short review of the ophthalmic literature of 1956. Appended is a list of hospitals in India where ophthalmic treatment is available, followed by a list of eye specialists in that country. The book (pp. 182) can be obtained from the Publishing House, 502, Narayan Peth, Poona.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Clinical Effects of Electrolyte Disturbances. Proceedings of a Conference held at the Royal College of Physicians of London February 27–28, 1959. Edited by E. J. Ross. (Pp. 210+x. 20s.) London: Pitman Medical Publishing Co. Ltd. 1959.

Zwanglose Abhandlungen aus dem Gebiet der Normalen und Pathologischen Anatomie. Edited by Professor Dr. W. Bargmann and Professor Dr. W. Doerr. Vol. 6. ***Zur Orthologie und Pathhologie der Hoyer-Grosser'schen Organe.*** By Julius Schorn, M.D. (Pp. 88; illustrated. DM. 22.) Stuttgart: Georg Thieme Verlag. 1959.

Frontiers in Cytology. Edited by Sanford L. Palay. (Pp. 529+xii; illustrated. 78s.) New Haven: Yale University Press. London: Oxford University Press. 1958.

La Biologie des Homogreffes. Colloques Internationaux du Centre National de la Recherche Scientifique. LXXVIII. (Pp. 284; illustrated. 2,200 fr.) Paris: Centre National de la Recherche Scientifique. 1958.

Elektrophysiologie des Gesichtssinns. Theorie und Praxis der Elektroretinographie. By Wolf Müller-Limmroth, M.D. (Pp. 331+vii; illustrated. DM. 59.) Berlin, Göttingen, Heidelberg: Springer-Verlag. 1959.

The Clinical Evaluation of New Drugs. Edited by S. O. Waife, M.D., F.A.C.P., and Alvin P. Shapiro, M.D. (Pp. 223+x. $7.50.) New York: Hoeber-Harper. 1959.

Principles and Practice of Obstetric Anaesthesia. By J. Selwyn Crawford, M.B., Ch.B., D.A.(England), F.F.A. R.C.S. (Pp. 128. 20s.) Oxford: Blackwell Scientific Publications. 1959.

Ceylon Hospitals Formulary, 1959. (Pp. 216.) Ceylon: Department of Health. 1959.

Neuropharmacology. Transactions of the Fourth Conference, September 25, 26, and 27, 1957, Princeton, N.J. Edited by Harold A. Abramson, M.D. (Pp. 285; illustrated. $5.) New York: Josiah Macy, Jr., Foundation. 1959.

Physiology of Prematurity. Transactions of the Third Conference, March 25, 26, and 27, 1958, Princeton, N.J. Edited by Jonathan T. Lanman, M.D. (Pp. 157; illustrated. $3.) New York: Josiah Macy, Jr., Foundation. 1959.

Introduction to Surgery. By Virginia Kneeland Frantz, M.D., Harold Dortic Harvey, M.D. Fourth edition. (Pp. 335+xiv. 48s.) New York, London: Oxford University Press. 1959.

Das Röntgenschichtbild des Ohres. The Tomogram of the Ear. By Professor Dr. Karl Mündnich and Dr. Kurt-Walter Frey. (Pp. 123+xii; illustrated. DM. 66.) Stuttgart: Georg Thieme Verlag. 1959.

Diseases of the Nose, Throat, and Ear. Edited by Chevalier Jackson, M.D., Sc.D., LL.D., L.H.D., F.A.C.S., and Chevalier L. Jackson, M.D., M.Sc., F.A.C.S. Second edition. (Pp. 886+xviii; illustrated. £7.) Philadelphia, London: W. B. Saunders Company. 1959.

Hypertension. The First Hahnemann Symposium on Hypertensive Disease. Edited by John H. Moyer, M.D. (Pp. 790+xii; illustrated. 98s.) Philadelphia, London: W. B. Saunders. 1959.

Trauma. By Harrison L. McLaughlin, M.D. (Pp. 784+xiii; illustrated. £6 6s.) Philadelphia, London: W. B. Saunders Company. 1959.

Textbook of Pediatrics. Seventh edition. Edited by Waldo E. Nelson, M.D., D.Sc. (Pp. 1,462+xxiv; illustrated. £5 15s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

Handbook of Diet Therapy. By Dorothea Turner. Third edition. (Pp. 222+xv. 37s. 6d.) Chicago: University Press. London: Cambridge University Press. 1959.

Dringliche Chirurgie beim Säugling und Kind. By Dr. H.-E. Grewe. (Pp. 180+xi; illustrated. DM. 25.) Stuttgart: Georg Thieme Verlag. 1959.

Catalytic Models in Epidemiology. By Hugo Muench, M.D., Dr.P.H. (Pp. 110+xi. 36s.) Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1959.

Fundamentals of Physical Chemistry. By H. D. Crockford and Samuel B. Knight. (Pp. 463+xvii; illustrated. 56s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall Limited. 1959.

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CONTROL OF ALDOSTERONE SECRETION

For many years it has been known that the adrenal glands exercise an important function in the control of electrolyte metabolism, and that adrenal insufficiency leads to depletion of water and salt associated with retention of potassium. At the present time the most potent adrenal hormone known to influence sodium metabolism is aldosterone, which was first isolated in 1952.[1] Excessive secretion of aldosterone from an adrenal neoplasm or from adrenal hyperplasia causes muscle weakness or paralysis, hypertension and renal dysfunction associated with hypokalaemia, mild hypernatraemia, and alkalosis—a syndrome which has been named after the Ann Arbor physician who first described it.[2] However, it is still not clear that all cases of Conn's syndrome are due to excess aldosterone production, because increased amounts of this hormone or its metabolites[3] have not always been found in the blood or urine, and it may yet be shown that there are other unidentified hormones in addition to aldosterone which influence electrolyte metabolism.

Some patients with oedema due to cardiac, renal, or hepatic disease also excrete excessive amounts of aldosterone. Although it would be naive to think that aldosterone is the sole cause of sodium retention in these disorders, its possible importance in this connexion has led to much research into the mechanism by which the secretion of aldosterone is regulated. In this and last week's issues Drs. D. A. Denton and J. R. Goding and Professor R. D. Wright have described their carefully and elegantly conducted experiments in sheep which throw much light on this problem. Their findings confirm much of the earlier work done in Switzerland and the United States, and are complementary to the important discoveries made independently by two groups of American investigators.

There is good evidence that aldosterone secretion, unlike that of other adrenocortical hormones such as cortisol, is largely independent of adrenocorticotrophin (A.C.T.H.) secretion from the anterior pituitary.[4–7] On the other hand, changes in sodium, potassium, or water content of the body have a profound effect, and increased amounts of aldosterone are secreted as a consequence of restricting sodium intake,[8 9] excessive sweating,[10] in salt-losing nephritis,[11] and after loss of blood.[12] It is clear from Denton's work that this response is not due to any alteration in the sodium concentration of the blood perfusing the adrenal glands, but is related to changes in volume of the extracellular fluid. Thus, increasing the volume of extracellular fluid reduces aldosterone secretion, and reducing the volume by loss of either sodium or water increases aldosterone secretion.[13 14]

These findings suggest that aldosterone secretion is regulated by volume receptors which in turn control the adrenal output of aldosterone by means of some humoral mechanism. The experiments in which Denton transplanted the adrenal gland to the neck show that neural control of the gland plays no part in this regulation, and that there must be a humoral substance distinct from A.C.T.H. which controls aldosterone secretion. Similar results have been obtained in cross-circulation studies in dogs.[15] Constriction of the inferior vena cava increases the output of aldosterone, and if blood from an animal in which this is being done is perfused through the adrenal gland of a normal dog the amount of aldosterone formed increases rapidly and falls again when cross-circulation is stopped. Until recently the site of origin of this trophic hormone was unknown —although clearly it was not the anterior pituitary, because aldosterone secretion may be normal after hypophysectomy—nor was the nature or location known of the receptors which monitored the volume of extracellular fluid. The investigations of G. L. Farrell[16] suggest that the neurohumour is elaborated in the diencephalon, particularly in the area of the pineal and subcommissural body. In amphibians which spend their lives in salt water and on dry land the pineal body is a modified third eye, and it would be fitting if it were confirmed that this structure is concerned with "seeing" that the salt content and hence the volume of extracellular fluid of the body are maintained within normal limits.

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The nature and site of the volume receptors are still under investigation. Localized changes of blood volume in the area of the right atrium and supradiaphragmatic portion of the inferior vena cava influence the production of aldosterone.[17,18] Section of the vagus does not prevent the rise in the secretion of aldosterone that follows constriction of these structures, but the expected fall in the output of aldosterone when the constriction is released does not occur if the vagus nerves are cut.[19] This suggests that stimuli which diminish aldosterone secretion follow vagal pathways, but those which increase it do not. Aldosterone output can also be modified by slight alterations of pulse-pressure in the lower part of the carotid arteries, and this effect can be prevented by denervation of the carotid bifurcation. Further work is required to confirm these findings and to apply the results of these animal experiments to man, but it seems likely that useful information will be gained about the formation of oedema in cardiac failure and other conditions associated with sodium retention.

ORAL TREATMENT OF PERNICIOUS ANAEMIA

The oral treatment of pernicious anaemia with extracts of stomach mucosa dates from 1930, when J. F. Wilkinson in Britain and W. B. Castle in the U.S.A. introduced desiccated hog-stomach preparations made from whole mucosa and given in a dose of 15–30 g. (0.5 to 1 oz.) daily. This treatment was very successful, and patients kept well for years on their daily dose of this unappetizing powder. In 1949 Wilkinson[1] was able to report that out of 441 patients treated only with desiccated hog's stomach for six years or more only 15 had relapsed, and this was because they had neglected treatment: they responded again when they took their proper dose. After vitamin B_{12} was identified as the "extrinsic factor" it was shown that the action of the "intrinsic factor" in gastric juice was to enable the vitamin B_{12} to be absorbed in the intestine, and so it seemed reasonable to suppose that a mixture of vitamin B_{12} together with a suitable preparation of intrinsic factor made from stomach mucosa would be effective when given by mouth. Though parenteral vitamin B_{12} is entirely satisfactory, there is a place for oral treatment, since it saves doctors', nurses', and patients' time, and some patients dislike repeated injections. The techniques for making active preparations of intrinsic factor from hog's stomach or duodenum were already well known, and commercial tablets containing 5–15 μg. of vitamin B_{12} and 15–30 mg. of an extract containing intrinsic factor soon became available from several sources.

Surprisingly enough, these tablets have given disappointing results in the long run. The patients respond excellently at first; the red cells and the haemoglobin level rise, the general condition improves, and restoration of health takes only a few weeks. But, after periods varying from six months to two years the blood count begins to fall and macrocytosis reappears. Increasing the daily dose of the mixture containing vitamin B_{12} and intrinsic factor is sometimes temporarily effective, but sooner or later the patient appears to have become quite resistant to this treatment. When he is given vitamin B_{12} by injection the blood count promptly returns to normal and can be kept so indefinitely with regular treatment. Elsewhere in this issue (p. 535) Dr. E. K. Blackburn and his colleagues at Sheffield report once again similar experience with a preparation of vitamin B_{12} and hog's duodenal or pyloric mucosa, and they have watched their patients for periods of $2\frac{1}{2}$ years or more. Out of 13 patients previously being treated by injections of vitamin B_{12} but transferred to this oral treatment 5 were found to have subnormal levels of vitamin B_{12} in the serum—that is, less than 150 $\mu\mu$g./ml.—after $2\frac{1}{2}$ years, and eleven after $3\frac{1}{2}$ years. Only 2 of these patients had actual haematological relapses with a falling red-cell count and return of macrocytosis. Nine patients with pernicious anaemia were treated from the beginning with this preparation of vitamin B_{12} and intrinsic factor: they showed satisfactory initial responses, but one relapsed after $2\frac{1}{2}$ years, and after five years a satisfactory concentration of vitamin B_{12} was found in the serum of only two.

It is not certain what the minimum level of vitamin B_{12} in the serum should be to ensure normal haemopoiesis and continued normal health, but a form of treatment that leads to subnormal levels in so high a proportion of patients is clearly unsatisfactory. Similar results showing that vitamin B_{12} absorption becomes progressively less after treatment for a few months with tablets containing fractions of hog's mucosa have been obtained by others, notably M. Schwartz, P. Lous, and E. Meulengracht[2] in Copenhagen. Schwartz[3] did in fact show that an intrinsic-factor-inhibiting substance could be detected in the serum of many patients given oral treatment, and such inhibitors were not present before treatment. K. B. Taylor and J. A. Morton[4] at Oxford have been able to prepare rabbit antisera

[1] Wilkinson, J. F., *Lancet*, 1949, **1**, 291.
[2] Schwartz, M., Lous, P., and Meulengracht, E., ibid., 1958, **2**, 1200.
[3] ——, ibid., 1958, **2**, 61.
[4] Taylor, K. B., and Morton, J. A., *J. Path. Bact.*, 1959, **77**, 117.
[5] Heathcote, J. G., and Mooney, F. S., *Lancet*, 1958, **1**, 982.
[6] Castle, W. B., ibid., 1958, **2**, 270.

specific against human intrinsic factor and against hog intrinsic factor, so there is little doubt that intrinsic-factor preparations from gastric mucosa can be antigenic.

At the haematological congress held earlier this month in London, Schwartz went so far as to state that *all* the commercial preparations of vitamin B_{12} and intrinsic factor on the market were unsatisfactory and should be withdrawn until it has been discovered how to make them effective but without this antigenic property. Since extracts of desiccated hog's stomach made from whole mucosa are known to have been successful for so many years, the key may well be found by studying them more closely. Schwartz thinks that the ratio of vitamin B_{12} to intrinsic factor may be critical, and it may be important not to have more than a minimum of intrinsic factor present. Another possible method of obtaining a suitable non-antigenic preparation of intrinsic factor has been suggested by the experiments of J. G. Heathcote and F. S. Mooney,[5] who used a material claimed to have intrinsic-factor activity that was derived from a bacteriological source. Unfortunately their experiments were not designed in a manner to carry conviction or to eliminate the possibility that the vitamin B_{12} alone was responsible for the haematological changes observed. Castle[6] emphasized that experiments with a single dose of vitamin B_{12} of not more than 5 μg. should be carried out, and, if Heathcote and Mooney's "peptide complex" is effective in such experiments, this preparation may be the answer to the problem. In the meantime the practitioner who wishes to give oral treatment to his patients with pernicious anaemia should keep to the well-tried preparations of proteolysed liver or desiccated mucosa of hog's stomach.

DETECTION OF DIABETES

At a Joint Meeting of Endocrine Societies held recently in London, Dr. Joan Walker reported the results of a diabetes survey initiated by the British Diabetic Association.[1] This survey was made in a large Midland village. Specimens of urine passed after a high-carbohydrate meal were submitted for testing by over 80% of the population of 5,400.[2] When glycosuria was detected, a glucose-tolerance test was carried out. There were 33 known diabetics in the village and another 25 mild symptomless cases were detected in the course of the survey. This suggests that the true incidence of diabetes in Great Britain is about 12 per 1,000, and that for every known case there is another as yet undetected and untreated. Previous surveys in this country and in the United States have given similar results.[3 4]

It may be questioned whether anything is gained by detecting cases of mild symptomless diabetes. The results of serial studies made in the American community of Oxford, Mass., suggest that these mild cases tend to become progressively more severe.[5] If this is so, control of the hyperglycaemia should slow down the rate at which the disease progresses and also lessen the risk of complications. Untreated diabetes in the older age groups may cause chronic infection or ulceration of the feet and vascular and retinal changes. If anything can be done to reduce the incidence of these complications it should be given serious consideration. The treatment required is not unduly arduous. These patients are nearly all obese and middle-aged or elderly; most will respond to suitable dietary restriction, while a few will require oral hypoglycaemic drugs as well. Reduction of weight is important and likely to be beneficial quite apart from reduction of blood sugar. Admittedly, obese, middle-aged women are apt to waver from a strict reducing diet, but the fact that "sugar" has been found often gives them the necessary stimulus to heed their doctors' advice.

If the detection and treatment of latent diabetes is desirable, how are the cases to be found? "Diabetes detection drives," in which people are asked to bring specimens of urine to testing stations set up in public places, are an accepted practice in the United States. In Great Britain the first moves in detection of diabetes are initiated by the family doctor. He has to decide when to ask the patient for a specimen of urine for testing. The early symptoms of diabetes include thirst, polyuria, nocturia, and in women pruritus vulvae. Many patients getting on in years do not like to worry their doctors with mild symptoms. In others the hyperglycaemia and glycosuria do not give rise to any symptoms. The general practitioner has to be on the alert for patients who are likely to have symptomless or almost symptomless diabetes. Three things should always be regarded with suspicion—obesity, a family history of diabetes, and, in women, a history of having had big babies.

The first step in the detection of latent diabetes is to test a specimen of urine passed two hours after a high-carbohydrate meal. Testing the urine for sugar is a very simple matter these days if the glucose oxidase test papers are used. This method is specific for glucose, though false-positive results may be obtained if the specimen is brought in a bottle that has contained glucose or hydrogen peroxide. When

[1] Walker, J. B., *J. Endocr.*, 1959, **18**, xviii.
[2] —— *Postgrad. med. J.*, 1959, **35**, 302.
[3] Wilkerson, H. L. C., and Krall, L. P., *J. Amer. med. Ass.*, 1947, **135**, 209.
[4] Cochrane, A. L., and Miall, W. E., *Proc. roy. Soc. Med.*, 1946, **49**, 261.
[5] Wilkerson, H. L. C., Krall, L. P., and Butler, F. K., *J. Amer. med. Ass.*, 1959, **169**, 910.

the result of the test is positive, the diagnosis should be confirmed by estimations of blood sugar, and if the patient has no diabetic symptoms a glucose-tolerance test is advisable. In many cases the results will be unequivocal, but in some doubts remain and it is necessary to take into account such things as the method used for estimating the glucose and whether it was done with capillary or venous blood. The most informative point on the curve is probably the 2-hour figure, and if this is over 120 mg. per 100 ml. it is very suspicious.

Diabetic surveys in Britain and elsewhere have shown that for every known diabetic there is another undetected case. If these are found and treated by simple measures, the progress of the condition will be slowed and the risks of unpleasant complications reduced. The detection of cases of latent diabetes is a challenge to the family doctor.

WATER INTOXICATION

R. Emery[1] recently reported the case of a woman who became confused, began vomiting, and progressed to convulsions and coma as a result of drinking a large volume of water. T. J. Carter[2] saw a man admitted unconscious to a casualty department, where he had six major fits in succession, and again the immediate diagnosis was water intoxication. The first patient was an alcoholic psychopath who aimed to drink 30 pints, and the second a schizophrenic who perhaps drank large quantities of water because of his delusions. Over 20 years ago H. S. Barahal[3] reported a schizophrenic woman who drank water to the point of intoxication in an effort to wash away the poison she believed she was being given. Compulsive water-drinking, on the other hand, usually as part of an hysterical illness, does not lead to intoxication unless antidiuretic hormone is given, in the belief that the condition is one of diabetes insipidus.[4] A. G. Swanson and O. A. Iseri[5] recently reported two cases of water "encephalopathy": one patient drank large quantities of water because of a sudden unquenchable thirst, and the other, who also gave himself enemas, because of a great and unsatisfiable urge to defaecate.

Water intoxication is not confined to the mentally abnormal. It may follow over-enthusiastic washouts of a colostomy,[6] or of the rectum, or excessive intravenous therapy, especially after operations,[7] and particularly in children,[8] with whom the permissible margins of error are smaller. It is a cause of coma in hypopituitarism,[9] and may result from a diuresis test in adrenal cortical insufficiency or after administration of posterior pituitary extracts. It can in fact arise in so many different ways that it is one of the diagnoses to be considered in any patient presenting with fits or in coma, or with restlessness and vomiting, or with an acute episode of mental abnormality—if the history does not definitely exclude it. Water intoxication results not only from excessive intake, but also from normal intake with deficient excretion, and in a totally anuric patient even the water formed in the metabolism of a high-fat diet may tip the patient into the water-intoxicated state.

Patients with diabetes insipidus have been known to excrete 43 litres of urine in 24 hours[10]—an average of 30 ml. per minute—but a more normal maximum rate of urine excretion is 20 ml. per minute[11] or 1,200 ml. (approximately 2 pints) an hour. Anyone drinking at the rate of more than two pints an hour is therefore a candidate for water intoxication. If, in addition, he has a degree of renal dysfunction (as from chronic nephritis), or is somewhat depleted in sodium, whether through heavy sweating, a low-salt diet, or a salt-losing syndrome, the onset of symptoms is all the more likely. Endocrine abnormality—lack of hydrocortisone or excess of antidiuretic hormone—also interferes with the renal elimination of water.

The excessive water is predominantly (two-thirds) intracellular, so that palpable oedema is rare. However, a pint of water (568 ml.) weighs a pound and a quarter (568 g.), so that the patient is abnormally heavy. There is one cardinal biochemical sign always present: the serum sodium is always low (below 120 mEq/litre according to V. Wynn[7 12]). This probably reflects extracellularly the intracellular dilution which is the immediate cause of the cerebral dysfunction. In uncomplicated water intoxication other findings in the blood (serum potassium and urea and packed cell volume) are within normal limits. Clinically, pulse and blood pressure are normal, and the only physical signs may be extensor plantar responses with hyperactive tendon reflexes. The electroencephalogram is not helpful. Treatment may be expectant, by withholding fluids, or transfusions may be given with hypertonic glucose or hypertonic saline (up to 12%), which will reduce intracellular over-hydration promptly. Cortisone may help in promoting renal function if there is any suggestion of adrenal cortical insufficiency.

The most important point about water intoxication is that it tends to crop up unexpectedly in odd ways and unusual situations. Its symptoms are individually very unspecific and predominantly neuropsychiatric. When the onset is gradual, lethargy, apathy, and sleepiness, leading on to nausea and vomiting, form the picture. With acute onset, "strange behaviour, loss of attention, confusion, staring aphasia, incoordination, and sleepiness interspersed with periods of violent behaviour"[12] and, later, fits, coma, and overbreathing may be seen. The elderly, children, and mental defectives are probably the groups most vulnerable. Water

[1] Emery, R., *Brit. med. J.*, 1959, **2**, 190.
[2] Carter, T. J., ibid., 1959, **2**, 367.
[3] Barahal, H. S., *Psychiat. Quart.*, 1938, **12**, 767.
[4] Barlow, E. D., and de Wardener, H. E., *Quart. J. Med.*, 1959, **28**, 235.
[5] Swanson, A. G., and Iseri, O. A., *New Engl. J. Med.*, 1958, **258**, 831.
[6] Clayton-Jones, E., *Brit. med. J.*, 1959, **2**, 306.
[7] Wynn, V., and Rob, C. G., *Lancet*, 1954, **1**, 587.
[8] Baskin, J. L., Keith, H. M., and Scribner, B. H., *Amer. J. Dis. Child.*, 1952, **84**, 351.
[9] Wynn, V., and Garrod, O., *Brit. med. J.*, 1955, **1**, 505.
[10] Weir, J. F., Larson, E. E., and Rowntree, L. G., *Arch. intern. Med.*, 1922, **29**, 306.
[11] Smith, H. W., *The Kidney*, 1951, New York.
[12] Wynn, V., *Metabolism*, 1956, **5**, 490.

intoxication is a neglected subject, and it would be helpful to have more detailed descriptions of the psychological signs during its course, relating the mental phase to the patient's excess weight and to the levels of serum sodium found at different times.

LOWER MATERNAL AND INFANT MORTALITY IN SCOTLAND

Perhaps the most impressive evidence of medical achievement during the past quarter-century has been the reduction of maternal mortality. The extent of the achievement is strikingly illustrated in a recent examination of Scottish statistics by C. A. Douglas and P. L. McKinlay.[1] In 1921 there were slightly more than six maternal deaths per thousand live births, and the rate remained virtually unchanged until the mid-thirties. It then declined regularly to about one death in 2,000 live births in 1957. In England and Wales the death rate to-day is about one-eighth of that in the pre-war years. This is a point worth bearing in mind in discussions of the Cranbrook Report.

It is not possible to give a complete explanation of these changes. Every cause of death shows some reduction, but Douglas and McKinlay estimated that two-thirds of the maternal lives saved in Scotland between 1931–3 and 1952–7 were attributable to a reduction in mortality from puerperal sepsis, eclampsia, accidents of childbirth, hyperemesis gravidarum, and placenta praevia. Unfortunately it is only for puerperal sepsis that we have evidence, from notifications, of the relative importance of a decline in morbidity and a decline in case mortality. It shows there has been a sharp fall in case mortality from about 1935, and it can be attributed confidently to treatment by sulphonamides and antibiotics. But a decline in the numbers of notifications, which began a few years earlier, is more difficult to explain. In part, no doubt, it is due to improved preventive measures, but other influences may also have acted.

These difficulties in understanding what appears to be a straightforward problem suggest the need for caution in interpreting the trends of other causes of death. It was not difficult for Douglas and McKinlay to show that changes in maternal age, parity, social class, and geographical distribution—all of which are known to be related to the outcome of pregnancy and childbirth—can have had little influence on the trend of mortality since 1935. It is more difficult to be precise about the factors that did. In at least one important disease—hyperemesis gravidarum—there has been no significant advance in knowledge of aetiology or treatment. At present we can only speculate about the possible effect of improved maternal health, better antenatal care, and changes in obstetric practice. The advance has been impressive, but so long as it does not rest on a secure knowledge of aetiology we cannot be complacent, and Douglas and McKinlay rightly stress the need for further investigation of the more important causes of maternal death. These are now eclampsia, phlegmasia alba dolens and embolism, and post-partum haemorrhage.

The trend of Scottish stillbirth and infant mortality rates has also been favourable, and in 1957 they were only slightly higher than the corresponding rates for England and Wales. Infant mortality has declined largely because of the successful attack on infectious disease, and as a result perinatal mortality (stillbirths plus deaths in the first week of life) deserves special attention. In Scotland in 1957 it accounted for more than three-quarters of the stillbirths and deaths of infants under 1 year old. There has also been a change in the significance of different causes of death. To-day the outstanding problems are unquestionably prematurity and congenital abnormalities, which, with a group of ill-defined causes, are responsible for a high proportion of the perinatal mortality. It has been estimated that premature births comprise about half the stillbirths and neonatal deaths, and, though in many cases the prematurity is secondary to other causes, a considerable proportion of the deaths, particularly those occurring after birth, have no such explanation; the birth of the infant in an immature state appears to be the primary cause of death. Congenital abnormalities also are of outstanding importance, and are beginning to attract the attention they deserve. Indeed, what uniquely characterizes these two important causes of perinatal mortality is that they appear to be unresponsive to the general improvements in obstetric practice, maternal health, and standard of living which have had so profound an effect on other causes of foetal and maternal death. Everything that we know about premature births and congenital abnormalities suggests that their prevention is unlikely to be a secondary consequence of some general trend, and can be brought about only through increased understanding of their aetiology.

[1] Douglas, C. A., and McKinlay, P. L., *Hlth Bull. (Edinb.)*, **1959**, **17**, 17.

INTESTINAL DIVERTICULA

The two articles on intestinal diverticula in recent issues of this *Journal* differ in their approach to the subject. Mr. J. K. McCollum[1] reviews some of the problems met with among the patients with intestinal diverticula over the course of nine years. Duodenal diverticula are not uncommon, but they are usually symptomless. Occasionally they may cause dyspepsia or gastro-intestinal bleeding, and McCollum records two examples of haematemesis and melaena. He also describes two patients with acute complications of jejuno-ileal diverticulosis: one of them had fatal haematemesis and melaena, while the other had acute peritonitis secondary to acute diverticulitis. Unlike diverticula of the small intestine, colonic diverticula are a familiar cause of symptoms in everyday clinical medicine, and McCollum analysed the features in 90 such patients. In the absence

[1] McCollum, J. K., *Brit. med. J.*, 1959, **2**, 34.
[2] Edwards, H. C., *Postgrad. med. J.*, 1953, **29**, 20.
[3] Yeager, G. H., *Amer. Surg.*, 1956, **22**, 611.
[4] Badenoch, J., and Bedford, P. D., *Quart. J. Med.*, 1954, **23**, 462.
[5] Dick, A. P., *Brit. med. J.*, 1955, **1**, 145.
[6] Watkinson, G., Feather, D. B., Marson, F. G. W., and Dossett, J. A., ibid., 1959, **2**, 58.
[7] Cameron, D. G., Watson, G. N., and Witts, L. J., *Blood*, 1949, **4**, 793.
[8] Drexler, J., ibid., 1958, **13**, 239.

of complications the condition is not dangerous to life, but with rupture or acute infection there is a risk of death from peritonitis or acute suppurative pericolitis. Massive haemorrhage, intestinal obstruction, and fistula formation are other serious complications. Because diverticulosis of the large bowel is potentially dangerous, as McCollum's article made plain, some surgeons are now resorting more readily than in the past to elective resection of the affected part of the bowel while the symptoms remain mild, choosing a quiescent phase whenever possible.[2 3]

During recent years much interest has been aroused by the finding that massive jejunal diverticulosis may be associated with steatorrhoea and a megaloblastic anaemia.[4 5] A case of this type was reported by Dr. G. Watkinson and his colleagues.[6] Impairment of intestinal absorption of the same nature as is associated with jejunal diverticulosis may accompany an intestinal stricture or a "blind loop" of intestine created surgically, such as is often done in the treatment of Crohn's disease. It has also been shown experimentally in the rat that the formation of a blind loop of intestine which is kept filled by peristalsis is followed by the occurrence of a macrocytic anaemia.[7] The suggestion has been made that stagnation of the intestinal contents in any of these conditions is likely to allow coliform organisms to flourish and that in turn these impede absorption by some mechanism which is as yet uncertain. There is already evidence that the anaemia and malabsorption can be mitigated, at least partly, by the administration of antibiotics. The special interest of the patient described by Watkinson and his colleagues is that surgical resection of the affected part of the jejunum was followed by complete recovery of intestinal function and by a return to normal of the blood picture. This demonstrates beyond all reasonable doubt that the jejunal diverticula were indeed responsible for the total clinical disturbance, even though the exact mechanism by which they exerted their harmful influence remains obscure. So far as the failure to absorb vitamin B_{12} is concerned, a recent study by J. Drexler[8] showing that indole compounds inhibit the utilization of vitamin B_{12} by micro-organisms is relevant because such compounds are known to be produced by coliform bacteria.

NEW EYE DISEASE IN INFANCY

Cytomegalic inclusion disease is a virus disease about which something has been learnt in recent years. The inclusion bodies were first noted, fairly commonly, in the cells of the salivary glands of normal adult animals in many species. Subsequently a species-specific filterable virus transmissible to newborn or young animals was isolated; adults could not be infected, presumably because they already suffered from asymptomatic infection. There were occasional exceptions to the benign course of this infection, for a lethal strain of the virus was observed in mice and guinea-pigs.

In man many of the features seen in animals were found. In children dying from any cause the incidence of inclusion bodies in the salivary glands ranged from 12 to 32% in different series, though only a small percentage showed the presence of inclusions throughout the body tissues. General dissemination of the virus, as shown by the presence of inclusion bodies, is more often seen in adults who have died from debilitating diseases. Among these debilitating diseases, in children or adults, whooping-cough and virus pneumonia have been outstanding, and it has become clear that the disease is protean in its manifestations. A presumptive diagnosis of cytomegalic inclusion disease can be made on the presence of periventricular calcification in the brain as shown by radiography in a patient, especially a child, with an acute ill-defined disease, while the diagnosis can be confirmed on finding cells laden with inclusion bodies in the urine.

The clinical picture as understood at present is of a disease in newborn or young infants, who are generally underweight and frequently premature. The systemic character of the disease shows itself by fever, jaundice, with enlarged spleen and liver, and anaemia and other blood disturbances such as thrombocytopenia, petechiae, and a tendency to bleeding. The infants often have pneumonitis or gastro-enteritis, and radiography shows cerebral calcification. That there are ocular symptoms has become increasingly clear in recent years. In 1947 B. Kalfayan[1] detected the disease post mortem in a 1-month-old baby with necrotic membranous conjunctivitis which had eroded the sclera and ciliary body. More recently a patch of choroiditis was recorded in another case clinically[2]; dacryo-adenitis has been observed in a woman aged 59 possibly also suffering from this disorder.[3] To these scattered reports R. P. Burns[4] has now added a case of progressive uveitis in a full-term infant weighing only 3½ lb. (1.6 kg.) at birth. At 3 months of age the clinical appearance of the disease was fairly typical; this subsided, but by 6 months of age hydrocephalus and mental retardation were apparent. At the height of the infection multiple patches of acute choroiditis, with inflammatory reactions in the vitreous and anterior segment, could be seen as a progressive disturbance ending ultimately in pigmented scars in the choroid, with secondary optic atrophy. The urine showed cells with typical cytomegalic inclusions. Of particular interest in this case was the finding that aqueous withdrawn from the anterior chamber at the height of the attack produced in tissue culture inclusions similar to those previously isolated from the urine. Burns stresses the value of examining the urine and of a skull radiograph in any case of uveitis in a child. Laboratory tests for antibodies could not be of much use because the infection is presumably widespread in the general population and becomes clinically manifest only under exceptional conditions. At present the task seems to be to show not so much that the virus is present in the body as that it is active. It would also appear that the protozoal disease toxoplasmosis, which causes similar damage to the eye as well as cerebral calcification, is often associated with the virus of cytomegalic inclusion disease.

[1] Kalfayan, B., *Arch. Path. (Chicago)*, 1947, **44**, 467.
[2] McElfresh, A. E., and Arey, J. B., *J. Pediat.*, 1957, **51**, 146.
[3] Mietke, H., *Klin. Mbl. Augenheilk.*, 1955, **127**, 400.
[4] Burns, R. P., *A.M.A. Arch. Ophthal.*, 1959, **61**, 376.

Clinicopathological Conference

A FATAL CASE OF PAROXYSMAL HAEMOGLOBINURIA

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with paroxysmal haemoglobinuria who died at Hammersmith Hospital aged 47 (Case No. 184,722; P.M. No. 8,300).

Clinical History

Dr. M. D. MILNE: This patient was perfectly healthy until the age of 33. He was then serving in the British Army in Italy, and had an attack of haemoglobinuria after swimming. There were no further attacks for six years, but from 1950 until his death in 1958 there were frequent and prolonged periods of severe haemoglobinuria. During this time he was always anaemic and mildly jaundiced. The haemoglobinuria was usually worse at night and in the early morning, but was sometimes continuous throughout the whole day. The attacks were often more severe after upper respiratory infections.

Until his last admission to hospital the haemoglobin averaged 8 g./100 ml. of blood and there was a constant reticulocytosis of 20–35% of the circulating red cells. The serum bilirubin averaged from 1.5 to 3 mg./100 ml., but there was no bilirubinuria. The mean red-cell survival time estimated by the radio-chromium method was

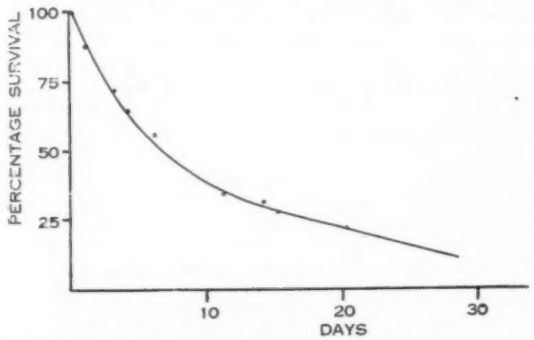

FIG. 1.—Erythrocyte survival curve, as measured with ^{51}Cr. The mean cell life-span was calculated to be approximately nine days.

nine days (Fig. 1). Tests for acid haemolysis of red cells were positive and were considered diagnostic of paroxysmal nocturnal haemoglobinuria. He was treated throughout by oral iron, blood transfusion being thought unnecessary and undesirable.

TERMINAL ILLNESS

In January, 1958, he had an attack of acute bronchitis which was associated with rapid and serious deterioration. There was increased haemoglobinuria and jaundice, with severe anaemia and depression of the white cell and platelet counts. The haemoglobin was maintained by repeated blood transfusion of packed, washed cells, but the white cell count fell to 600/c.mm., the polymorphonuclear leucocytes being reduced to only 40/c.mm. The platelet count fell to 45,000/c.mm. Marrow aspiration showed that this was associated with a severe aplastic crisis complicating his prolonged haemolytic anaemia. There was severe collapse with a rapid, weak pulse, and the blood pressure fell to 90/60 mm. Hg. He had severe watery diarrhoea with resultant sodium and potassium loss. At this time serum sodium was 120 mEq/litre, serum potassium 3.7 mEq/litre, and serum bicarbonate 16.5 mEq/litre. Infusions of sodium lactate containing added potassium chloride resulted in some improvement. The abdomen was tympanitic and distended, with absent bowel sounds, and there was considerable hypogastric tenderness. A surgeon agreed that there was evidence of low-grade peritonitis but did not advise operation. The patient was treated with tetracycline by mouth and penicillin by injection with some apparent improvement. Further examination of the sternal marrow showed some improvement and there was a slight increase in the white cell count. Unfortunately, there was a sudden collapse one week after the beginning of the aplastic crisis and the patient died within 5 minutes.

Clinical Diagnosis

(1) Paroxysmal nocturnal haemoglobinuria.
(2) Aplastic crisis improving terminally.
(3) Paralytic ileus with low-grade peritonitis.
(4) Terminal basal bronchopneumonia.

Post-mortem Findings

Dr. B. E. HEARD: Necropsy was performed 23 hours after death. There were slender fingers and toes, long patellar ligaments (2¾ in.—7 cm.), and a high-arched palate—features of Marfan's syndrome. The abdomen was grossly distended. Post-mortem lividity was present posteriorly.

Respiratory System.—The mucosa of the trachea and main bronchi was congested. Both lungs were overweight (right 1,135 g., left 870 g.) from bronchopneumonia and inflammatory oedema. The basal segments of the right lower lobe were collapsed terminally. There was a small calcified tuberculous lesion in the apical segment of the left lower lobe. There was no evidence of pulmonary embolism. The right pleural sac was completely obliterated by dense fibrous adhesions. Bronchopneumonia was confirmed histologically and numerous colonies of Gram-positive cocci could be identified. Many alveoli were filled with fibrin but only moderate numbers of neutrophils were seen.

Heart and Great Vessels. — The pericardium contained about 30 ml. of straw-coloured fluid. The heart weighed 414 g. (normal maximum for a man of 5 ft. 11 in. (1.78 m.)=380 g.). The left ventricle was 18 mm. thick (normal=15 mm.), indicating slight hypertrophy. The other chambers and the tricuspid, pulmonary, and mitral valves appeared normal. The aortic valve was normal in circumference but there were adhesions involving 5 mm. of each side of the right posterior cusp. The aorta was very slightly hypoplastic in the gross but histologically normal. A section of the pulmonary artery was also normal. The coronary

arteries and aorta showed only a trace of atherosclerosis. All veins were normal.

Alimentary Tract.—The oesophagus and stomach were normal but loops of small intestine were distended by gas and lightly glued together by a small amount of yellow fibrinous exudate. A swab of this exudate yielded *Bact. coli*, and a histological section of jejunum showed that the wall was lightly infiltrated by lymphocytes, macrophages, and a few neutrophils. Some venules contained small thrombi which were associated with the infection and probably not the cause of it. Larger vessels supplying the small intestine were not blocked. The pelvic colon showed diverticulosis. The liver was slightly enlarged (2,382 g.) and had a rusty tinge. Perles's test showed iron at the periphery of each liver lobule and this was confirmed histologically. The iron deposit was light in relation to the renal deposit. There was no evidence of cirrhosis.

Kidneys.—Both kidneys were slightly enlarged (right 189 g., left 192 g.). The cortex was deepened and brown. Perles's reaction for iron was strongly positive in the cortex. The capsules of the kidneys stripped easily and the surfaces appeared smooth. Histologically there were heavy deposits of haemosiderin in the proximal convoluted tubules (Fig. 2) and in some of the loops of Henle. Glomeruli were mostly normal, but some had a small deposit of haemosiderin in the epithelium lining Bowman's capsule. A few tubules contained protein and sometimes a granular deposit of haemoglobin. Now and again a tubular epithelial cell filled with haemosiderin could be seen free in the lumen of an unaffected tubule. There was moderate fibro-elastosis of the arcuate arteries, but other vessels appeared normal. No thrombi were seen.

Spleen and Bone Marrow.—The spleen was slightly enlarged (204 g.). The pulp was soft and histologically contained scattered neutrophils. Perles's test was mildly positive. The vertebrae, ribs, sternum, and upper one-third of the right femur contained a "black-currant jelly" type of marrow which agreed with the clinical finding of an aplastic crisis. Histologically there was moderate cellularity, with myelocytes mixed with clumps of normoblasts (Fig. 3); neutrophils were scanty. In spite of the long history of haemolytic anaemia the red marrow in the right femur was mixed with fatty marrow in the middle one-third and did not extend into the lower one-third.

The *brain* weighed 1,635 g. (normal maximum = 1,450 g.), but no lesion was demonstrated in slices.

Pathologist's Diagnosis

(1) Paroxysmal nocturnal haemoglobinuria with gross renal siderosis.
(2) Bronchopneumonia.
(3) Aplastic crisis.
(4) Mild fibrinous peritonitis.
(5) Mild siderosis of liver and spleen.
(6) Marfan's syndrome.

Discussion

Professor J. V. DACIE: Paroxysmal nocturnal haemoglobinuria is a fascinating blood disease; it has been studied extensively, although it is very rare. I shall show first a blood film to emphasize that there are no characteristic features such as spherocytosis. The reticulocyte count is usually raised, giving rise to polychromasia, but generally speaking the red cells look normal, although some may be slightly macrocytic. The next slide (Fig. 4) is a photomicrograph of a bone-marrow biopsy film. The marrow is hyperplastic and most of the nucleated cells present are erythroblasts. A high-power view of the nucleated red cells shows that they are normoblasts, not megaloblasts.

As you have heard, this man's marrow became aplastic. The next slide (Fig. 5) gives an idea of what we found at the height of his crisis. The marrow is strikingly hypocellular; most of the cells present are reticulum cells or lymphocytes, and fat cells have reappeared. Here is a single nucleated red cell and here a mast cell. The last slide (Fig. 6) is of film made of marrow aspirated on the day he died. There is now definite regeneration. You can see quite a number of nucleated red cells and some promyelocytes, so it is a tragedy that he died just at this particular time.

CONFIRMATORY TESTS

I have two other slides to show you, both of which are significant from the point of view of diagnosis. This is a slide of urinary deposit stained by Perles's reaction to demonstrate ionized iron. This is so-called haemosiderinuria. Haemosiderinuria is a feature of this disease and was recognized as far back as 1911 by the Italian workers Marchiafava and Nazari. The next slide illustrates the so-called acid-serum test, which, if positive, is diagnostic of paroxysmal nocturnal haemoglobinuria. The essential lesion is an abnormal red cell; it is so abnormal that it undergoes haemolysis in normal serum. The haemolysis is, however, *p*H-dependent. If you collect serum in the ordinary way by letting blood clot, or by defibrinating blood, it loses carbon dioxide and becomes alkaline, the *p*H rising to about 8. If you add the red cells of a patient with paroxysmal nocturnal haemoglobinuria to serum at *p*H 8, you get little or no haemolysis on incubation. If, however, you expose the serum to carbon dioxide, as was done by Hijmans van den Bergh in 1911, or if you first add a small amount of acid such as hydrochloric acid to the serum to reduce the *p*H to 6.5–7.5, haemolysis will take place. In this particular experiment one-tenth volumes of different concentrations of acid were added. N/4 HCl caused the greatest haemolysis. If you add too much acid, haemolysis will be inhibited. The acid serum test seems only to be positive in paroxysmal nocturnal haemoglobinuria.

Professor J. MCMICHAEL: Was the "Marfan's syndrome" a pathological diagnosis or a clinical diagnosis?

Dr. MILNE: I am not sure whether the pathologists recognized it independently, but certainly it had not escaped Dr. Loughridge's eagle eye. The patient had the high arched palate and long fingers and toes typical of the syndrome. I did not mention it because we did not diagnose in life any of the important internal concomitants of Marfan's syndrome, and I thought it of no pathological importance and in fact was rather appalled when Dr. Heard brought it up.

WASHED CELLS FOR TRANSFUSION

Professor MCMICHAEL: Professor Dacie, would you like to tell us about the rationale of washing the red cells when transfusing patients with paroxysmal nocturnal haemoglobinuria?

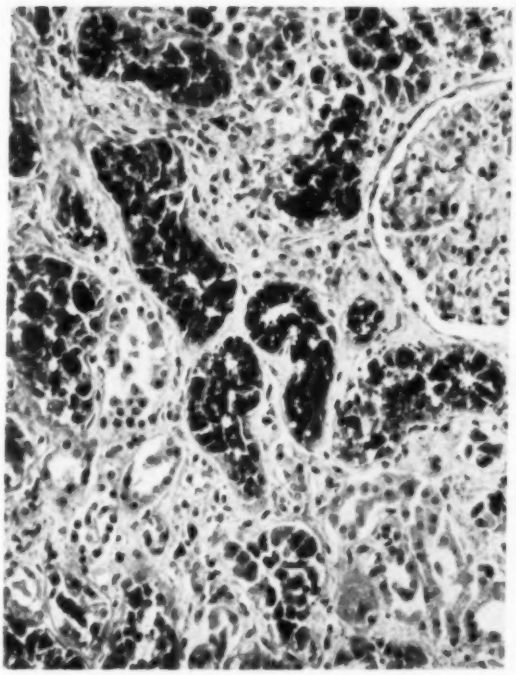

FIG. 2.—Section of kidney, showing heavy deposits of haemosiderin in proximal convoluted tubules. (×180.)

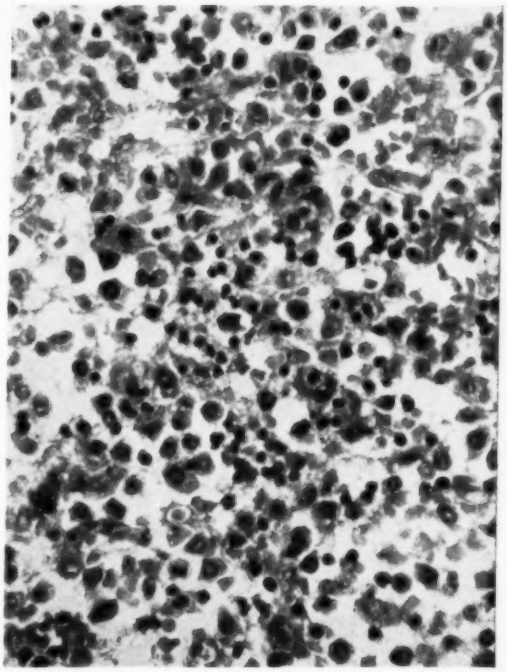

FIG. 3.—Section of marrow from a rib, showing several clusters of normoblasts (with small dense nuclei). (×440.)

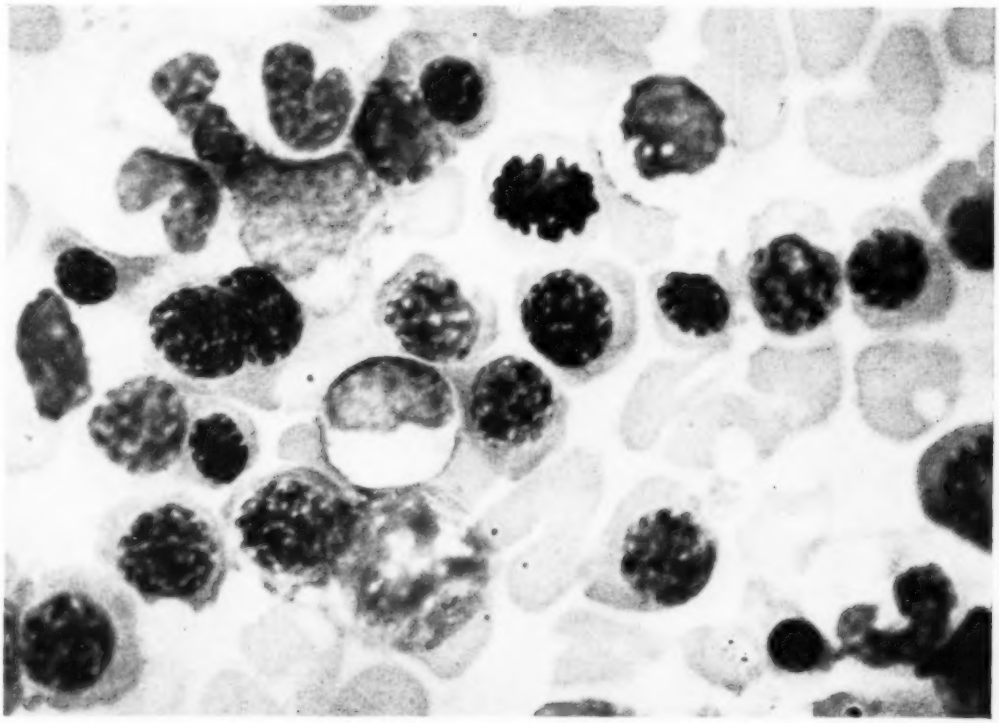

FIG. 4.—Marrow film two years before final illness, showing active erythropoiesis and also formation of granulocytes. (×1,530.)

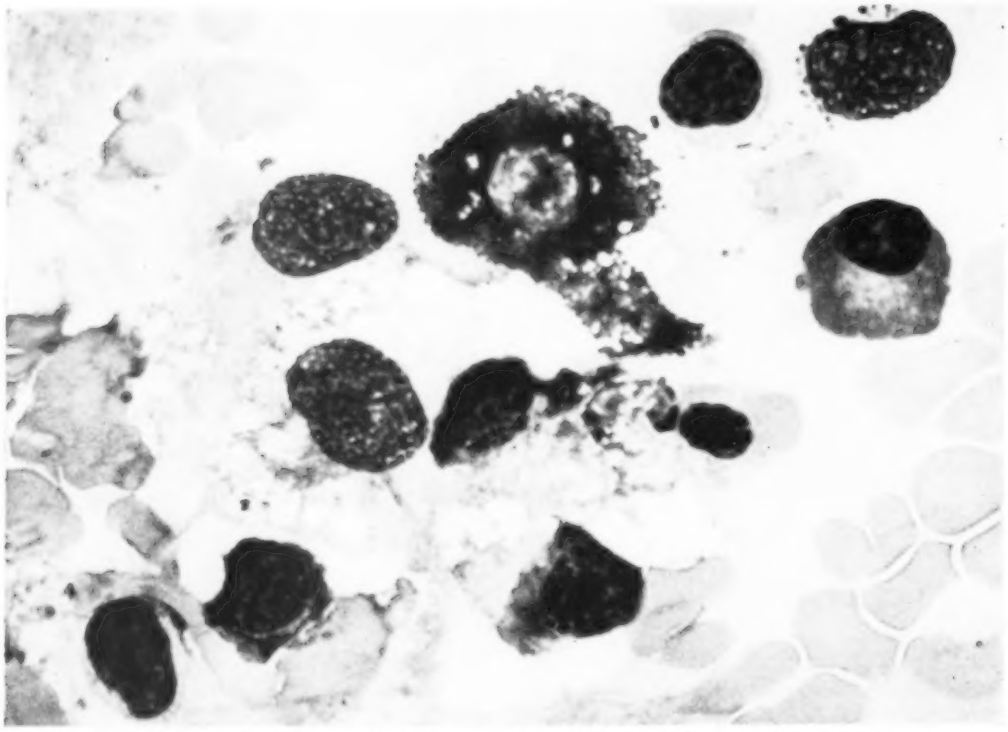

FIG. 5.—Marrow film one day before death, showing reduced erythropoiesis and absence of granulocyte precursors. Reticulum cells, plasma cells, lymphocytes, and mast cells are present in excess. (×1,530.)

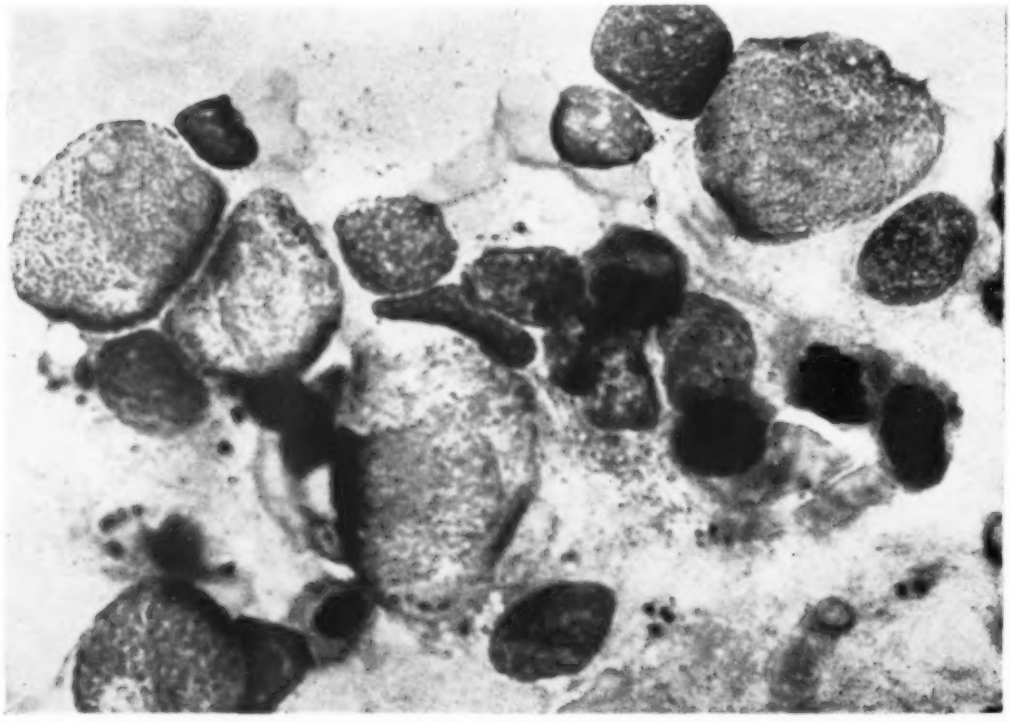

FIG. 6.—Marrow film made *post mortem*, showing the presence of promyelocytes (the large cells with granules in the cytoplasm). (×1,530.)

Professor DACIE: I think washing away the plasma with saline is useful, though why it should be is not certainly known. When the washing technique was first suggested, the idea was to remove plasma which might introduce some haemolytic factor the patient himself lacked. Now I think most people believe that the removal of plasma by itself is probably not important; in any case it is a very difficult thing to prove. The popular explanation is that the risk of reactions is reduced by removing leucocytes from the blood and that washed cells are useful only in patients who have received many transfusions. It seems that an almost inevitable complication of numerous transfusions is the formation by the recipient of iso-agglutinins against leucocytes and that it is the leucocyte–leucocyte agglutinin interaction which produces the reaction and pyrexia.

Dr. P. L. MOLLISON: I should like to comment on this. Although it was claimed some years ago (by Dameshek and others) that injections of plasma alone could induce severe febrile transfusion reactions, we have never been able to induce febrile reactions in this way, even in patients who regularly get bad febrile transfusion reactions. It has been suspected for almost 20 years that leucocytes in transfused blood can cause febrile reactions, but it has only recently been proved that they do so. Brittingham and Chaplin* have shown this very conclusively in a series of patients with a history of violent febrile reactions and with leucocyte agglutinins in their blood. When these patients were transfused with blood from which the buffy coat had been removed they got no reactions. The fact that in paroxysmal nocturnal haemoglobinuria haemolytic reactions sometimes follow the transfusion of compatible blood may merely indicate that in these patients any severe febrile reaction induces a haemolytic episode; the febrile reaction itself may well be due to transfused leucocytes.

Professor MCMICHAEL: Do you still wash the cells?

Professor DACIE: We still use washed cells for transfusions in our two other patients with paroxysmal nocturnal haemoglobinuria. They have had hundreds of transfusions and probably have leucocyte agglutinins in their serum. I think it is a good thing to do, but I admit the basis for the washing procedure has been slightly demolished by the passage of time.

Dr. C. L. COPE: One of the cases you mention, who has since had hundreds of transfusions, experienced a very severe reaction with his very first transfusion, before he could have built up any agglutinins against leucocytes.

Professor DACIE: I stand corrected. I had forgotten the incident, although I probably described it myself.

Professor MCMICHAEL: As a matter of experience it was found that they got on better with washed cells.

Professor DACIE: Yes; in both patients. We have been maintaining them in this way for many years. Though it is fair to say that the first serious reaction was observed in the other patient—a group-A patient who was given group-O blood. I am sure that the explanation for the very severe reaction she experienced was the transfusion of anti-A, not necessarily of high titre, in the blood she received. One of the phenomena of the disease is a unique sensitivity of the patient's cells to iso-agglutinins such as anti-A or anti-B. The patient's cells are haemolysed by these antibodies, whereas normal cells are usually only agglutinated.

*Brittingham, T. E., and Chaplin, H., *J. Amer. med. Ass.*, 1957, **165**, 819.

CAUSE OF DEATH

Dr. C. PALLIS: Are you satisfied, Dr. Heard, that the cause of death has been fully explained? Perhaps there was no single factor. The aplastic anaemia was beginning to improve: his red cells were being replaced by transfusion. The low-grade fibrinous peritonitis does not sound severe enough to have killed him. Clinically the pulmonary infection seems to have been improving also. The electrolyte disturbance had been corrected. Yet he collapsed and died very suddenly, it seems. Was this expected?

Dr. HEARD: The condition of the lungs was rather worse perhaps than I have led you to believe. There was severe bronchopneumonia and pulmonary oedema.

Dr. MILNE: He was very ill indeed. We were really expecting him to die for a week before he actually did, and we were just, on the last day, perhaps beginning to hope he would recover, when he abruptly died. He had a very severe acute abdominal illness and of course severe bronchopneumonia, and I should have thought that his cause of death is as well explained by these infective conditions as any. Very often, I think, the clinician can offer some sort of explanation as to the immediate cause of death more easily than the pathologist. The actual immediate cause of death is something which often shows no very obvious pathological features.

Professor MCMICHAEL: Pneumonia in a debilitated patient does cause circulatory collapse and death.

Dr. COPE: I imagine we could take it that the terminal rise in white cell count was a very puny response to the infection, probably the best the body could do.

Dr. MILNE: It is, I think, clear-cut in congenital haemolytic jaundice that these aplastic crises are very temporary and in fact much more temporary than any other aplasia of the marrow. This case seemed to be similar; if we could only have kept him alive for another two or three days, I think he would have got over it.

SPLENECTOMY

Professor MCMICHAEL: Why did the spleen fail to undergo considerable enlargement in a relapsing haemolytic anaemia like this?

Professor DACIE: I think the answer is that the nature of the abnormality of the red cells is such that they break down in the circulating blood stream, and that there is no predilection for haemolysis within the spleen. The haemolysis is not brought about by phagocytosis by reticulo-endothelial cells, and it doesn't seem to depend on an auto-antibody mechanism. The spleen is usually quite small and usually impalpable. Splenectomy does not help the course of the disease except perhaps fractionally.

Professor MCMICHAEL: As a corollary to that, would you say that in any haemolytic anaemia where the spleen is big splenectomy might help?

Professor DACIE: I think it depends on what the histology of the spleen is. If it is full of lymphadenomatous tissue, I think the answer is no: if it is full of red cells which have been filtered off from the circulation, I think the answer is yes, splenectomy will help.

Professor McMICHAEL: Can you in fact divide your own material roughly into these patterns?

Professor DACIE: As shown in America and also by Dr. P. L. Mollison here, we can get this information by seeing where radioactive chromium is deposited in a patient with a haemolytic anaemia whose cells have been tagged with radioactive chromium. If the chromium leaves the blood and goes into the spleen, this strongly suggests that the spleen is causing the haemolysis, or most of it.

Dr. COPE: Is it known where the envelopes of the cells go when haemolysis occurs. Are they filtered out in the spleen, or is that not known?

Professor DACIE: I certainly don't know for certain. I should think that they are taken out of the blood stream by the spleen, liver, and lymph nodes, etc. One typical complication this patient didn't have in life and didn't show *post mortem* is thrombosis. Thromboses often occur widely and are the commonest cause of death in paroxysmal nocturnal haemoglobinuria; they may start on the basis of these cell envelopes.

STEROID AND ALKALI THERAPY

Dr. COPE: Is steroid therapy of any value?

Professor DACIE: Probably no. There may be a temporary rise in the reticulocytes and perhaps a rise in haemoglobin, but I am sure from a long-term point of view steroid therapy is not worth while. We were afraid of giving steroids to this particular patient, although they might have stimulated his marrow, because of the presence of infection.

Dr. COPE: There is another question that I should particularly like to ask you, for I know you have got an answer. As the haemolysis occurs at acid *p*H, why cannot these patients be maintained with advantage on alkalis?

Professor DACIE: We have not tried alkalis here. There are descriptions in the literature of how alkalis in very large doses have been given. Haemolysis was apparently restrained, but only temporarily. When the patients were taken off alkalis, they developed haemolytic crises. It seems as if the sensitive cells which had accumulated in the blood stream were destroyed almost all at the same time when the alkali therapy was stopped.

THE CARDIAC HYPERTROPHY

Professor C. V. HARRISON: Can we attribute the cardiac hypertrophy to a prolonged hyperdynamic circulation resulting from anaemia? Was the degree of anaemia sufficient?

Professor McMICHAEL: Well, it was hypertrophy of the heart all right. Cabot in his book *Facts on the Heart* reported hearts of 600 g. in patients who died of prolonged chronic anaemia. I don't think the aortic valves were terribly significant in causing hypertrophy, do you, Dr. Goodwin?

Dr. J. F. GOODWIN: I wouldn't have thought so, no, because any leak must have been terribly small if no diastolic murmur was heard. Blood pressure was normal and there were no peripheral signs. I would have thought not.

Professor McMICHAEL: We occasionally see clinically insignificant adhesion of aortic valve cusps in the necropsy room in almost anybody. Do you think this is due to a form of rheumatism?

Professor HARRISON: There may be many people in whom a rheumatic process starts but fails to progress. But I think it's much better to say we don't know.

Dr. COPE: There is one other point about the iron metabolism. The amount excreted as granules in the urine may be so great—up to 20 mg. or more a day—that the patients may be in iron balance even when they are having frequent large transfusions. This provides an outlet preventing the excessive accumulation of iron.

Professor DACIE: I think it is a very useful safety valve in patients who have to be transfused many times. This particular patient was transfused only during his last illness, I believe, and we thought at one time that he had iron deficiency from losing more iron in the urine than he was taking in by mouth. He had medicinal iron for this reason.

MARROW REACTION

May I ask Professor Harrison about one additional point? One of the things that struck me about the post-mortem findings was that his hyperplastic bone marrow extended downwards only to the middle of the femur. I should have been prepared to bet that it would have gone lower than that. Of course we have to realize that this is apparently an acquired disease. My question is this: In chronic anaemia, does one get very extensive marrow hypertrophy only in congenital disease? This patient had an acquired anaemia, which lasted for about 13 years. Nevertheless, this did not result in a maximum degree of hypertrophy of the marrow.

Professor HARRISON: I certainly confirm what you say about the hereditary diseases. They are quite outstanding. I truly can't remember what happens in acquired haemolytic anaemia, but I do remember what used to be said in acquired pernicious anaemia: there you have got red marrow right down to the bottom of the femur, so I don't think the acquisition of disease in adult life prevents your marrow hypertrophying right down to your ankles.

Professor DACIE: Do you think it is the nature of the disease which determines this? In paroxysmal nocturnal haemoglobinuria a relative marrow hypoplasia is in fact not uncommon as a chronic event. Some of the more anaemic patients seem to be anaemic not because they are destroying cells particularly rapidly but because they are not very good at regeneration. This particular patient seemed to be good at regeneration, for he usually had a high reticulocyte count. I was therefore surprised to see his marrow stop in the femur where it did.

Dr. MOLLISON: May I ask Professor Dacie another question? Does temporary marrow failure occur as a regular event in normal subjects during severe infection? Since the average life-span of normal red cells is about 110 days, even if all red-cell production stopped for as long as 10 days the haemoglobin concentration would fall by less than 10%. Thus temporary marrow failure could easily be overlooked in a subject whose red cells had a normal life-span, although, of course, if the red-cell life-span was short, failure of production for even a few days would cause a dramatic fall in haemoglobin concentration.

Professor DACIE: I really don't know the answer. Gasser,† the Swiss paediatrician, has described in

†Gasser, C., *Sang.* 1950, **21**, 237.

children as a not uncommon event what he calls "acute erythroblastopenia"; this has occurred in a variety of infections of different sorts, including virus diseases.

ROLE OF EXERTION

A VISITOR: Is very strenuous physical exertion recognized as an aetiological factor?

Professor MCMICHAEL: I saw a man the other day who had paralytic myoglobinuria which came on while climbing a mountain in the Lake District. His muscles were tender and the urine dark reddish brown.

Professor DACIE: I really don't know. However, I think it is possible that there is more than a casual association. One other patient I know also gave a very similar history of haemoglobinuria following bathing, and his disease also was ultimately shown to be paroxysmal nocturnal haemoglobinuria.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

British Medical Association

JOINT ANNUAL MEETING WITH THE CANADIAN MEDICAL ASSOCIATION, EDINBURGH, 1959

SUMMARY OF PROCEEDINGS

THE SECTIONS

SECTION OF PREVENTIVE AND SOCIAL MEDICINE

Monday, July 20

Aftercare of the Hospital Patient

Hospital and Community

With Sir KENNETH COWAN (Edinburgh), one of the joint presidents, in the chair, Professor T. FERGUSON (Glasgow) gave an account of an investigation based primarily on an unselected series of 705 men discharged from the general medical wards of four acute hospitals. Much devoted and highly skilled hospital treatment could have little prospect of restoring effective working capacity, for many patients on admission were already gravely, even hopelessly, ill. Convalescent accommodation, which had the express object of restoring capacity for work and bridging the wide gap between hospital ward and everyday life, was lamentably short. In Britain effective organized aftercare was yet only in its infancy so far as the common major illnesses of the people were concerned, and it badly needed development if the work of the hospital was not to be speedily undone. More must be done to help the family doctor in his struggle to keep the patient on his feet.

Progress after Hospital Treatment

Dr. R. W. F. HARNETT (Dundee) gave an interim report on a study similar to that of Professor Ferguson's which he was carrying out with Professor A. Mair. They had visited 300 male and 100 female patients at one, three, and twelve months after discharge from hospital, and a final visit at two years was planned. One object of their study was to demonstrate the effect on the subsequent progress of a patient of his medical management and also to assess his co-operation, insight, and understanding. Conclusions to date were that, where co-operation was lacking, 80% of patients had relapses. There was evidence that insight assumed some importance, particularly in patients with alimentary and cardiovascular diseases. Management rather than insight appeared to play a greater part in the progress of patients in the respiratory group.

Aftercare of the Elderly

Four case histories were used by Dr. I. M. RICHARDSON (Aberdeen) to illustrate some problems associated with, but not necessarily caused by, hospital-treated illness in old people. He suggested that there was a real need for an aftercare case conference committee in every sizable hospital and specially in those hospitals where elderly patients were cared for. Since the idea of these case conferences was to smooth the path from hospital to home there were four key people involved—the hospital consultant, the hospital almoner, the family doctor, and the local authority social worker (who might be a health visitor).

Aftercare of the Mental Patient

Preliminary findings were presented by Professor J. H. F. BROTHERSTON (Edinburgh) of an inquiry carried out in collaboration with three mental hospitals. All patients aged between 16 and 64 who had been discharged during an eight-month period were visited by a psychiatric social worker between one and two years later. Over a quarter of the patients had had to be readmitted to mental hospital one or more times in the interval since discharge. About a quarter were receiving further psychiatric out-patient treatment or were judged to be in need of treatment as either out-patients or in-patients. About one in six of the patients had financial problems which were serious or persistent or both. Of those who had previously been in paid employment, a half had remained in employment for at least 75% of the time between discharge and follow-up interview. Two-fifths of the patients were assessed as likely to benefit from services, other than the clinical psychiatric service, which the National Health Service might provide. Skilled home-visiting was the primary requirement. A quarter had social needs which might be met from services other than the National Health Service; these needs were most commonly work, social clubs, and recreative facilities.

Wednesday, July 22

Cancer Mortality in Canada

The joint president of the Section, Professor C. B. STEWART (Halifax, Nova Scotia), opened the session by introducing Professor JOHN WYLLIE (Kingston, Ontario), who gave the findings of a study of the comparative mortality index (C.M.I.) as applied to cancer mortality in Canada. During the period 1931 to 1957, for cancer of all sites combined, there was an upward trend in males and a decline in females. Of special interest was a steady rise in the C.M.I. for cancer of the pancreas, present in both sexes but seen especially in males.

Immunization Programmes in Canada

Canada's experience since 1925 in the prevention of communicable diseases through organized immunization programmes was reviewed by Dr. R. J. WILSON (Toronto). The recommended schedule was now as follows:

Age	*Immunizing Agent*
3 months ...	... DPT* polio vaccine, 1 ml. (3 doses at 4-week intervals)
Under 1 year	... Smallpox vaccine
12–18 months	... DPT polio vaccine, 1 ml.
About 3 years	... DPT polio vaccine, 1 ml.
About 5 years	... DPT polio vaccine, 1 ml.
Under 15 years	... Smallpox vaccine
Under 15 years	... DT† polio vaccine, 1 ml.
Over 15 years	... DT polio vaccine, 0.5 ml.

*DPT is diphtheria toxoid, pertussis vaccine, and tetanus toxoid combined.

†DT is diphtheria and tetanus toxoids combined.

Applied Epidemiology of Tuberculosis

Dr. A. J. NELSON (Vancouver, B.C.) made some observations on the applied epidemiology of pulmonary tuberculosis with special reference to British Columbia. Mortality was no longer a useful measure of prevalence, nor even were first admissions to sanatoria. The reservoir of cases in the community at any time was the important factor. Dr. Nelson advocated the study of case-finding indices. Thus, in evaluating the effectiveness of contact-tracing it was necessary to know the respective numbers of new active cases notified, contacts traced, new cases found in contacts, and, finally, new cases found per 1,000 contacts traced. Contacts traced per case were classified into household, close non-household, and casual. In mass miniature radiography surveys it was necessary to study the respective numbers of persons screened, new cases and new active cases found, and new cases and new active cases found per 1,000 screened. The yield of new active cases from both provincial and metropolitan mobile M.M.R. surveys was falling, and the Canadian public-health administrator would have to decide when these programmes became uneconomic.

Canada's National Sickness Survey

Dr. G. E. WRIDE (Ottawa) said that the main objects of the Canadian National Sickness Survey were to obtain estimates of the incidence and prevalence of illness of all kinds; the amount of medical and other health care received; the volume of family expenditure for the various types of health services; and the prevalence of permanent physical disabilities. A national survey which was not continuing in nature could be regarded as dealing only with a stated period of time which, unfortunately, receded rapidly into history. However, Dr. Wride thought that the current success of Canada's hospital insurance and other social assistance programmes was due in large measure to the accuracy of their preparatory estimates, which were based substantially on the analyses of the results of the Sickness Survey.

SECTION OF PSYCHIATRY

Monday, July 20

Psychological Medicine in Undergraduate Teaching

With Dr. T. P. REES (London), one of the two joint presidents, in the chair, Professor ALEXANDER KENNEDY (Edinburgh) opened a symposium on the place of psychological medicine in the medical curriculum by surveying present developments in undergraduate teaching at Edinburgh. The present emphasis in teaching was away from psychological medicine as a specialty, and many departments, including anatomy, physiology, social medicine, and divinity, took part in the effort to integrate ideas and practice. Professor Kennedy avoided psychodynamic hypotheses, and believed neurology should be the "grammar" of psychiatric teaching. He laid great emphasis on the experimental and clinical approach. Last year, for instance, 60 students had learned to hypnotize one another, there was an increased number of student clinical assistantships, and 160 had taken the fourth professional examination (psychological medicine), which included writing up a psychiatric long case as well as a 2½-hour written paper and an oral.

Psychiatric subjects were taught throughout the six-year course, beginning with the psychology of study in the first year and the measurement of human qualities in the second, and ending with child care and the psychology of medical practice in the final years. Lectures were less valuable than discussions, and 18 tutors took the students in groups of 5 and supervised the writing of case notes. In contrast, a survey he had just completed of the basic teaching in 25 British medical schools showed an almost complete reliance on lectures—for instance, normal psychology 12 lectures and 4 demonstrations, medical psychology 6 lectures, psychological medicine 20 lectures and 10 clinical demonstrations, plus a few attendances at in-patient and out-patient teaching sessions. There was rarely direct contact between student and patient.

Professor M. MILLAR (Aberdeen) said he had been trying for thirteen years to introduce students to normal psychology, using a variety of methods. The Goodenough Report (1944) had recommended teaching psychology along with anatomy and physiology as part of the 2nd M.B., but this failed in practice—partly because psychology was only allowed 25 hours of teaching time as against 250 hours for physiology and 900 hours for anatomy. While a department of psychological medicine ought to have the same numbers and quality of staff as other medical departments if it was to gain the necessary respect for its views, it was the mental set of the student on entrance and the whole ethos of the medical school which really settled the fate of psychology in the student's education.

Emotional Involvement

Professor J. S. TYHURST (Vancouver) described a scheme, now finishing its second year at the University of British Columbia, in which students in their first year of medicine (a four-year course) were assigned to selected families for a study of their psychological and social structure. The families were chosen by the public-health nurse from those attending a well-baby clinic; they were free of gross physical or psychological ill-health and willing to accept the visits of students. The students met regularly in groups of 6–8 with a tutor, who might come from paediatrics, public health, orthopaedics, or psychiatry, for case presentation and discussion on family dynamics, the social role of the physician, or anything connected with being a doctor. The tutors also met once a week with a psychiatric programme supervisor, and it was found that they suffered quite as much anxiety over the scheme as did the students. At the start people were unwilling to visit their allotted families, asked for detailed instructions what to do, and this was interpreted as anxiety over their degree of freedom. Then they began work and submitted anecdotal reports of their contacts, but soon again became hostile and critical—a second wave of anxiety. When this was surmounted they went back to work and began real interviews in which they tried to understand why, for instance, one man talked so much about football, or why another was involved in a particular marital situation. In Dr. Tyhurst's view learning could only proceed where there was emotional involvement, and the provoked anxiety was therefore valuable, provided it was worked through.

Dr. DENIS HILL (London) went back to the philosophical bases of psychiatric practice and of education in an attempt to diagnose the origin of the difficulties met with in trying to teach medical students in Britain about human behaviour. Medicine had achieved great successes in the physical field by eschewing teleology and relying on physiochemical determination, and the student was brought up to expect easily understood causal explanatory hypotheses. But hypotheses of this type failed in psychology and psychological illness, and this provoked anxiety or antagonism to their study. Because students were at present being trained and not educated, they could not tolerate doubt, ignorance, uncertainty. If they abandoned physiochemical determinism it was only to accept wholeheartedly the psychological determinism of psychoanalysis or the cultural determinism of Marxism. This would not change until there was a revaluation of hypotheses in medicine, until at the least students came into contact with patients from the very beginning of their studies.

Patients Make Good Teachers

Professor D. G. MCKERRACHER (Saskatoon) said his slogan was "Patients Make Good Teachers." Psychiatric teaching had to be based firmly on the care of patients if it was to succeed, and therefore each of his students was responsible for the diagnosis and treatment of 16 selected psychiatric out-patients in his last two clinical years, and in addition he had a month as a full-time clinical clerk

treating an in-patient under the general supervision of a resident, who in turn kept a staff psychiatrist informed.

Tuesday, July 21

Marital Breakdown

With Professor A. B. STOKES (Toronto), joint president of the Section in the chair, Dr. H. V. DICKS (London) spoke on "Some Aetiological Factors in Marital Crises." He and his collaborators had studied 157 disturbed marriages. They were compared with a control group of happy marriages. The marriage partners they had studied were predominantly of high social status and education: four-fifths owned their own houses and flats. Of 299 spouses, no fewer than 239 came from broken homes or homes with poor parental relations, where there was violence between the parents, temporary desertion, and so on. Only 4.2% of the spouses came from emotionally good homes. In contrast, in the matched control group, 54.6% came from good homes. The 299 spouses showed few overt neurotic symptoms, but disturbed parental relations in the home when the spouses were children seemed very important, and under certain conditions the spouses seemed to enact a compulsive repetition of their childhood experience. One of the conditions seemed to be their age. It seemed that marriages came to a crisis when the partners reached 35 or so, when the children were off to school. Dr. Dicks thought this mid-term crisis might be partly physiological (hormonal ageing), or partly the consequence of middle-class people becoming isolated within the family group and demanding more of marriage and family than they could give.

Brief Methods of Psychotherapy

Dr. D. STAFFORD-CLARK (London) then spoke on brief psychotherapy. Classical dynamic methods required the patient's attendance for a 50-minute interview 3–5 times a week for 40 weeks a year for four or five years, obviously an impossibility for the majority of patients. However, much could be achieved in a short while by deliberate technique. The first step was to establish good rapport. It was what the psychiatrist let the patient say, not what the psychiatrist said, which created rapport. The next step was for the physician to decide what the practical goals of treatment were, and how many interviews and what other measures would be needed to achieve them. In further interviews the patient's attention was directed to those topics needing special scrutiny. Acceptance, reassurance, insight, and training in voluntary relaxation and breathing control were the bases of the brief treatment given at Guy's.

Person and Family in Medical Education

The chair was taken by Dr. T. P. REES (London), the other joint president of the Section, while Professor G. R. HARGREAVES (Leeds) and Professor A. B. STOKES (Toronto) discussed aspects of medical education. Professor HARGREAVES said that when individual history-taking, the bedrock of psychiatry, revived with Freud, the family was looked on as a noxious agent, until the anthropological studies of Ruth Benedict and others showed how individuals were held together in a pattern of familial and other relationships imposed by their culture. Students had to be made aware of these many threads, and yet not blinded with their teachers' blindnesses. The present-day hospital was a bad place to learn family practice.

Professor A. B. STOKES (Toronto) said psychiatry had contributed to medicine as a whole by its emphasis on the patient as a person. The student was also a person. Teachers often had a stereotype of the medical student as someone made in their own image. A recent North American survey had shaken that illusion in its analysis of the medical students attending all United States medical schools. Forty per cent. of the students were married, and over 50% of them had at least one child, and over 25% had more than two. As students they were often supported by their wives, yet on the average they were $2,600 in debt when they qualified. These were factors which shaped their prejudices and outlook.

SECTION OF RADIOLOGY

Monday, July 20

Supervoltage Radiotherapy

With the joint president of the Section, Professor R. MCWHIRTER (Edinburgh), in the chair, Professor T. A. WATSON (Saskatoon) opened a symposium on supervoltage radiotherapy in malignant disease with cobalt-60. Supervoltage was not to be considered as a new concept in the treatment of cancer but rather as an improved technique for certain uses. It enabled adequate tumour-dose to be achieved with much simpler techniques than was possible with orthovoltage, and skin reactions were no longer a problem. Supervoltage rotational therapy had as its main advantages the simpler set-up and shorter daily treatment times. The provision of wedge fields, constructed for various angles, also permitted simpler treatment plans in some sites, particularly the larynx, in some skin cancers close to cartilage, and in carcinoma of the mouth. A disadvantage was the difficulty of shielding parts which it was not desired to irradiate.

In some tumours close to the surface, such as carcinoma of the lip, orthovoltage was to be preferred because of the lower depth-dose. Many tumours of the head and neck, such as carcinoma of the nasopharynx, were preferably treated by supervoltage irradiation to avoid the tumour-sparing effect of large bone-masses. Because, too, of the lesser absorption, tumours in bone, both primary and secondary, were better treated by supervoltage.

Cobalt-60 and Linear Accelerators

Dr. IVAN H. SMITH (London, Ontario) reviewed the use of cobalt-60 in the treatment of oral cancer in the first 50 patients treated on a radical basis by means of the original 1-kilocurie Eldorado unit. Five main conclusions could be drawn: (1) Tumour invasion of the mandible could be controlled. (2) Complete regression of disease recurring after previous treatment was possible. (3) Nodes which were the site of metastases and which could be included within the treatment beam for the primary tumour could be controlled. (4) A very low incidence of bone necrosis was found. (5) There was no skin reaction, and mucosal reaction too was less. Occasionally high tumour-resistance was found, but of the 50 patients treated by the machine 19 had been free of tumour for periods ranging from 39 to 83 months. Further experience had been gained with the rotating hectocurie Theratron junior using both rotation and wedge fields, either alone or in conjunction with fixed fields. In general, although the fixed field gave a somewhat better depth-dose with less integral dose and less penumbra, rotation offered an easier technique with no need for plaster fixation.

Dr. RALSTON PATERSON (Manchester) showed a colour film illustrating the main techniques suitable for radiotherapy at megavoltage levels. The study was based on work with the Metropolitan-Vickers 4-MeV linear accelerator, but the techniques were equally applicable to mass cobalt units of appropriate design. Three main techniques had been found to be of use. The first was most suitably employed with small fields using beam direction and with fixation of the patient, as in the treatment of tumours of the head and neck. Alternatively one could work at a constant focal-spot to tumour distance of 100 cm. Here angled fields could be used as in the now standard treatment by three fields of carcinoma of the lung or bladder. Thirdly, the machine could be used at a treating distance of more than 100 cm. The use of wedge filters was of great importance in megavoltage radiotherapy.

Professor B. W. WINDEYER (London) discussed the place of supervoltage radiotherapy in the treatment of carcinoma of the fauces and alveolus. Experience had shown that supervoltage gave better eradication of disease and better palliation of incurable disease. It was especially suitable for treating tumours involving the mouth and throat, and he stressed the value of arc rotation on the cobalt-60 apparatus. The majority of the lesions were treated by this method and a lesser number by means of fixed fields on the linear accelerator. The various supervoltage machines were complementary. The cobalt-60 apparatus was more convenient for rotation therapy and the linear accelerator was preferable when a sharper beam was wanted.

Radiodiagnosis

Hyperplastic Cholecystoses

With the joint president of the Section, Professor A. C. SINGLETON (Montreal) in the chair, Professor A. JUTRAS (Montreal) read a paper on hyperplastic cholecystoses and their cholecystographic manifestations. He thought hyperplastic cholecystoses (gall-bladder conditions which were proliferative and degenerative in nature rather than inflammatory or neoplastic) should not be included in the miscellaneous group of so-called chronic cholecystitis because a more precise diagnosis could lead to better treatment. The three main conditions were cholesterolosis, neuromatosis, and adenomyomatosis. Cholesterolosis was characterized by abnormal deposits of cholesterol esters forming pin-point yellow specks (strawberry gall-bladder) and polyps or pseudo-papilloma, at times solitary but more often multiple. Radiography to demonstrate these lesions had to be of a high standard and should include films taken with compression and at high kV. Neuromatosis indicated the proliferation of the autonomic nervous elements. Adenomyomatosis was defined as an excessive superficial expansion of the mucous membrane together with pouch-like formations (intramural diverticulosis) passing through the much thickened muscular layer. The condition could be shown radiologically as a smooth, fundal filling defect with or without the formation of diverticula. A combination of these three conditions induced the gall-bladder to over-concentrate the dye and expel it too quickly.

Excretion Pyelography

Dr. C. J. HODSON (London) dealt first with the value of excretion pyelography as a means of assessing renal function, and secondly described what information might be obtained from alteration in the size of the kidney as shown by means of pyelography. Conditions must be properly controlled if pyelography was to be used to measure function. The intake of fluid prior to the examination was of major importance, since the density of the pyelogram was directly proportional to the amount of water excreted with the contrast medium. The nephrotic syndrome was often associated with kidneys of normal size, but if the renal shadows were enlarged diabetes insipidus or a later stage of nephritis might be suspected. With small kidneys the third stage of chronic nephritis or obliterative arterial disease had to be considered. If the output of urine was diminished, there might be obstruction to the ureter, localized chronic pyelonephritis, or a systemic reaction to the contrast medium.

The main object of excretion pyelography was to show the size and shape of the kidneys. Usually both kidneys were the same size, the same shape, and showed the same pelvi-calicine pattern. Moreover, the thickness of the renal substance was the same. Dr. Hodson demonstrated the radiographic findings in several cases of chronic pyelonephritis showing local decreases in kidney substance corresponding to the areas of renal damage and subsequent fibrotic scarring. There was close correlation between the radiological findings and the eventual pathological specimens.

Facial Injuries

In a paper on the radiological aspects of facial trauma Dr. E. F. CRUTCHLOW (Montreal) stressed the importance of teamwork in diagnosis. The force of acceleration or deceleration, the resilience of the opposing forces, and the area of application all influenced the severity of facial fractures. Dr. Crutchlow made a strong plea for the universal use of safety belts in automobiles. Other safety precautions should include padded dashboards, the elimination of sharp objects, and the use of padded caps or crash-helmets. Recognition of the symmetry of the facial landmarks greatly assisted in the interpretation of radiographs, and he suggested that the posterior wall of the maxillary antrum could be outlined by the insufflation of radio-opaque powder.

Pulmonary Hypertension

Dr. R. G. GRAINGER (London) divided cardiac diseases characterized by elevated pulmonary vascular pressure into two distinct groups. The first consisted of those in which the pulmonary artery pressure was raised either by an increased pulmonary blood flow (hyperkinetic) or by an increased peripheral resistance (obstructive). Hyperkinetic states (e.g., septal defects, patent ductus, etc.) were all characterized by a large right ventricle, large main pulmonary arteries, and a vascular plethora of the peripheral lung fields. The size of the main pulmonary artery was more dependent on pulmonary blood flow than on pulmonary arterial pressure. Plethora was a manifestation of a large pulmonary blood flow and not of arterial hypertension. Oligaemic lung fields with large main pulmonary arteries indicated an obstructive arterial hypertension.

The second group of cases consisted of those with elevated pulmonary venous and capillary pressures. Pulmonary and pleural oedema, with thickening of the fissures and effusions, were manifestations of a pulmonary capillary pressure above 25 mm. Hg. Interstitial pulmonary oedema often preceded clinical evidence of left heart failure and could be diagnosed radiologically by the presence of visible interlobar septa—A and B lines of Kerley. When acute alveolar oedema complicated chronic pulmonary venous hypertension it tended to spare the lung bases. This was because of diminished blood flow through them consequent on the narrowing of the basal arteries and veins in response to the high pressure in the basal veins. This diversion of blood resulted in enlargement of the upper-lobe veins which could be recognized radiologically.

SECTION OF RHEUMATIC DISEASES

Thursday, July 23

Symposium on the Polyarthritic Syndrome

With Dr. W. S. C. COPEMAN (London) in the chair, Professor E. G. L. BYWATERS (London) discussed the problem of acute polyarthritis. He emphasized the difficulty and the importance of making a firm diagnosis in the early, acute stage. In spite of the falling incidence of rheumatic fever, it was probably the most common form of acute polyarthritis in Britain. In the early stage, culture of the throat for haemolytic streptococci or the presence of a positive anti-streptolysin O titre might be an important aid. He found the Rose–Waaler test less helpful. Treatment should be directed towards the cardiac lesions in rheumatic fever and towards the joints in the other forms of arthritis.

Professor J. H. KELLGREN (Manchester) discussed chronic polyarthritis. The terms chronic polyarthritis and rheumatoid arthritis used to be practically synonymous, but the development of agglutination tests, designed to estimate the titre of the specific rheumatoid macroglobulin, had helped to define rheumatoid disease more accurately. Diagnosis had become more precise and prognosis therefore more certain for the individual case.

Dr. D. C. GRAHAM (Toronto) spoke on ankylosing spondylitis. Most Canadian physicians now considered it to be a separate entity from rheumatoid arthritis. The incidence was highest in males. In two-thirds of the cases the onset was insidious, the majority complained of back pain, and about 15% had acute peripheral joint involvement. The fundamental treatment was a strict regime of rest combined with controlled exercises and maintenance doses of salicylates. Phenylbutazone was a useful adjunct. Deep *x*-ray therapy was helpful for pain, but it did not cure the disease and had dangerous side-effects, such as leukaemia.

Short Papers

The chairman, Dr. J. F. L. WOODBURY (Halifax, Nova Scotia) introduced Dr. F. P. DEWAR (Toronto), who spoke on the problem of painful feet. He considered that 80% of painful foot troubles began in the fore-foot. After the acute stage deformity was the main trouble and was generally due to atrophy or malfunction of the small muscles of the foot. He emphasized that patients should be referred early for surgical opinion, as minor orthopaedic procedures could be extremely helpful in painful foot deformities.

Dr. J. S. CRAWFORD (Toronto), in discussing the principles of rehabilitation for the arthritic patient, emphasized the importance of complete bed-rest in the acute phase. Well-moulded rest-splints should be applied and maximum movement of all joints performed twice daily.

Dr. R. J. G. SINCLAIR (Edinburgh), in discussing diagnostic problems in a rheumatism clinic, described the classification of 5,781 patients examined over the last ten years. Seventy-two per cent. had articular involvement, while in 23% the symptoms were considered to be non-articular in origin. Although the remaining 5% presented with musculo-skeletal pain the primary disorder was found to be elsewhere than in the musculo-skeletal system. Selected cases illustrating some of the difficulties and problems of diagnosis were presented. Physicians should be very careful before labelling their difficult cases with the term "rheumatism" or "psychoneurosis."

Dr. G. D. KERSLEY (Bath) discussed current views on gout. Treatment fell into four categories: advice on general regime and avoidance of trigger factors; physical management during and between attacks; the medicinal control of acute attacks with colchicine and phenylbutazone; and the use of the uricosuric drugs, salicylates, probenecid, "longacid," and G.28315 ("anturan"). Of these four uricosuric drugs, anturan appeared to be more potent without troublesome side-effects. Its effectiveness did not appear to be impaired after two years' treatment. It was indicated in hyperuricaemia or if attacks increased in frequency. It should be supplemented by colchicine for the first six weeks and by phenylbutazone for the first few days of the attack.

Dr. A. G. S. HILL (Stoke Mandeville) described laboratory tests and prognosis in rheumatoid arthritis. He considered that the prognosis in any one individual case could not be predicted with accuracy. The Rose–Waaler test (or one of the related serological reactions) gave useful guidance, especially if repeated several times.

Panel on Treatment of Rheumatic Diseases

The chairman, Dr. A. W. BAGNALL (Vancouver), introduced the panel members. For the relief of pain Professor R. E. TUNBRIDGE (Leeds) considered the salicylates extremely valuable, small doses of codeine as in tab. cod. co., *B.P.*, helpful, but pure codeine and pethidine inadvisable. The toxic effects of gold therapy were not negligible and death from agranulocytosis might ensue many years after the last-administered dose. Dr. F. DUDLEY HART (London) thought that steroid therapy should not be started unless full basic conservative measures were available. Deep *x*-ray therapy produced lasting effect in ankylosing spondylitis, and the danger of leukaemia might be due to excessive dosage.

Dr. J. N. SWANSON (Toronto) considered phenylbutazone a very useful drug in selected cases and found few side-effects at a daily maintenance dosage level of 200–300 mg. The main danger was unpredictable gastro-intestinal bleeding. Professor F. S. BRIEN (London, Ontario) discussed the indications and benefits of intra-articular hydrocortisone therapy, which he felt were limited. Dr. BAGNALL spoke briefly on his six-and-a-half years of experience in the use of the chloroquine group of drugs. He was convinced of their efficacy.

SECTION OF TROPICAL MEDICINE

Thursday, July 23

Anaemia in the Tropics

With the president of the Section, Sir ALEXANDER BIGGAM (Edinburgh) in the chair, Dr. R. H. GIRDWOOD (Edinburgh) opened the discussion on anaemia in the tropics. He dealt in particular with the macrocytic anaemias.

Megaloblastic anaemia was caused by deficiency in vitamin B_{12} or folic acid, or both. An important factor was the destruction of folic acid by cooking. The uncooked diet of a low-income-group Indian might contain 91 μg. of folic acid: after cooking there might be 7.85 μg. The corresponding figures in Britain were 106.2 and 56.3, and folic-acid deficiency was rare. Other causes of megaloblastic anaemia were pregnancy, malabsorption, malaria, and bleeding. Pyrimethamine was a folic-acid antagonist and could cause megaloblastic anaemia when given over a period.

Indian troops seen by Dr. Girdwood west of the Brahmaputra had iron-deficiency anaemia, and those seen east had megaloblastic anaemia. The causes were probably sprue, dietary deficiency, and malaria acting on men who had an initial mild iron-deficiency anaemia. The conclusion to be drawn from many published observations was that there was a multiplicity of factors which had to be untangled before the true cause of a macrocytic anaemia could be established.

Iron-deficiency Anaemia

Professor A. W. WOODRUFF (London) said that this was a major health problem in the tropics. Of 40 unselected male and 40 female patients examined in Nagpur, half the males and all but seven of the females had haemoglobin values of less than 10.15 g.%. Of 1,151 deliveries there in 1954, 178 of the mothers had a haemoglobin value of less than 8 g.%, and in 39 the value was less than 3 g. It was the same in other parts of India.

There was no evidence of a widespread iron-deficiency in the diets of tropical peoples to explain the prevalence of iron-deficiency anaemia. Interference with iron absorption by phytates was of doubtful importance: more important was the bulk of tropical diets. Bacterial infections could cause microcytic hypochromic anaemia, and malaria was an important cause of anaemia. And yet, although no patients with malaria were seen in Mauritius in 1953, the incidence of anaemia had almost doubled. Unless the diet of a woman of child-bearing age contained approximately 20 mg. of iron a day there would probably be a negative iron-balance. Growing children also were very precariously balanced.

Abnormal Haemoglobins

Dr. H. LEHMANN (London) discussed the problems in recognizing and classifying abnormal haemoglobins. The most important method in the differentiation of haemoglobin variants was that of electrophoresis, but this technique was fallible. The time was approaching when it would be possible to define a haemoglobin variant on the basis of its

molecular structure. Meanwhile, however, more general procedures would have to be applied.

As a temporary solution, until an actual chemical classification of haemoglobins could be produced, the following general nomenclature had been proposed by Agar, Lehmann, and Vella. They divided the haemoglobin into two major groups : foetal and adult variants—the former showing an ultra-violet spectrum of the foetal type and including haemoglobin F, the pigment of Fessas and Papaspyrou, "Bart's," and "Alexandra." The adult variants were divided into six groups according to their electrophoretic behaviour on paper electrophoresis at alkaline *p*H.

Dr. A. B. RAPER (Bristol) spoke of the vigorous growth of information on abnormal haemoglobins during the last ten years. The *British Medical Journal* had been a vehicle for many reports, and its well-informed leading articles were receiving world-wide recognition. There were only four haemoglobinopathies of widespread clinical importance: diseases associated with haemoglobins S, C, E, and with thalassaemia. Sickle-cell disease could be homozygous (sickle-cell anaemia) or heterozygous when associated with haemoglobin C or thalassaemia.

The chance observation by Griffiths in 1955 that sickling was inhibited by biscoumacetate ("tromexan") was a promising start in treatment. Special interest centred upon trait carriers because they held the key to the question of why the sickling gene was conserved despite its consistent depletion through homozygous deaths. All the best evidence favoured the hypothesis that trait carriers were protected against *falciparum* malaria.

Sickle-cell Disease in West Africa

Professor G. M. EDINGTON (Ibadan) said that in West Africa about 30% of the population were carriers of the haemoglobin S or C traits. The incidence of haemoglobin C was highest in Northern Ghana and the Haute Volta region; it declined towards the east, south, and west. As C declined S rose, so that the combined incidence of the two remained at approximately 30%. The most common types of diseases were sickle-cell anaemia and sickle-cell haemoglobin C disease. Sickle-cell thalassaemia, however, was not a rarity.

One special problem of sickle-cell disease was the selection of donors for blood transfusion. Of 6,335 donors 34 with haemoglobin SC disease and 15 with haemoglobin C disease had been discarded, but sickle-cell trait blood was accepted. However, Professor Edington felt rather worried about the use of this blood for exchange transfusion in severe anaemias of pregnancy. There was no doubt that the abnormal haemoglobins imposed a heavy burden on a transfusion service in a country where the incidence was high, as in Nigeria.

Friday, July 24

Tropical Diseases Outside the Tropics

With the president of the Section in the chair, Professor B. G. MAEGRAITH (Liverpool) opened the discussion by describing his experience of malaria in the United Kingdom. There was a great deal of it immediately after the second world war, and there was a recurrence after the Korean campaign. It was not sufficiently appreciated that benign tertian malaria relapsed when the preventive drug was stopped. A patient's geographical history was important. Malignant tertian malaria was often misdiagnosed as influenza. It was always worth eradicating malignant tertian malaria: energetic treatment with any schizonticide was effective. Whether it was worth treating benign tertian malaria had to be decided on individual merits. Malaria was still indigenous to this country: in Warrington there had been a case of *vivax* infection in a man who had never been abroad but who lived near an American airport.

Amoebiasis

Sir GEORGE MCROBERT (London) discussed amoebiasis. "The parasite was of no import unless an import"—indigenous strains being non-pathogenic. 2% to 5% of people in Britain were carriers of indigenous *Entamoeba histolytica*. In the tropics the parasite could live as a commensal in the gut contents, with no tendency to invade the tissues, but in circumstances not yet fully understood it could eat its way into the mucosa and submucosa. Vegetative forms might find their way into capillaries and venules, reaching liver, lung, and brain. It was still not possible to differentiate between pathogenic and harmless strains by means of the microscope, but forms producing cysts or less than 10 μ in diameter were non-pathogenic. The number of cases notified from 1949 to 1956 was just under 50 per annum. In 1957 the figure was 63, and in 1958, 170. Immigrants from Pakistan, Africa, and the Caribbean increased the number of infections detected. The relatively high death-rate among cases notified must mean that milder infections were not reported.

Any treatment might cause a temporary disappearance of cysts, but it was not safe to exclude amoebiasis unless three stools were negative, one passed after a purge. Unless the patient was exposed to reinfection, amoebiasis had a good prognosis and was a curable disease. Fatal results could ensue in exploration of the liver by needling if preliminary treatment by emetine was not given. Emetine bismuth iodide was still the best eradicator, but there were now new amoebicides on the market which could be given to ambulant patients.

Filariasis

Professor W. E. KERSHAW (Liverpool) said that of several hundred of filariae half-a-dozen lived in man. It was likely that tropical eosinophilia was a filarial disease due to an aborted infection with animal filariae. The most important thing was that filariasis could be controlled; it was no longer out of hand. The diagnosis of filariasis must be kept in mind when people from the tropics were being examined. Professor Kershaw knew of a Nigerian student who had complained of "worms moving under the skin," and had been diagnosed as a schizophrenic.

Intestinal Helminths

Dr. F. J. WRIGHT (Edinburgh) said that the only common intestinal worm in this country was the threadworm, and there was a danger that a complaint of worms might be considered synonymous with threadworms, and treated ineffectively. The most common intestinal helminth, other than the threadworm, brought to this country from the tropics was the hookworm. Adult forms could survive untreated for many years. Ascaris was often symptomless in light infections, but might be a factor in urticaria or even asthma, as well as the explanation of eosinophilia. Strongyloides was long considered relatively non-pathogenic, yet discomfort and, at times, distress were caused to sufferers by the creeping eruptions. The most effective treatment was the newly introduced drug dithiazanine iodide ("telmid").

Taenia saginata and *Taenia solium* were acquired from raw or uncooked beef or pork respectively. *T. saginata* from beef was much the more common. So harmless was it that in countries such as Kenya, containing both meat-eating and vegetarian tribes, the possession of a tapeworm could be taken as a hallmark of good nutrition. Treatment with *Filix mas* or mepacrine was effective.

T. solium produced little more disturbance than *T. saginata* in the adult stage, but the larva gave rise to cysticercosis. The numerous cysts in muscles produced no disability, but when scattered in the brain they could cause death. The symptoms were most commonly fits. If, however, the patient could be tided over this stage by sedatives and anticonvulsants, he could survive, and the fits, after a time, could cease. Increased intracranial pressure, due to swelling and absorption of the cysts when the larva died some five to seven years after invasion, had to be relieved surgically.

SECTION OF UROLOGY

Monday, July 20

Calcium Metabolism in Renal Calculi

After a short address by a vice-president, Mr. DAVID BAND (Edinburgh), welcoming members to the Western General Hospital, the meeting continued under the chairmanship of the joint presidents, Mr. ARTHUR H. JACOBS (Glasgow) and Dr. W. K. KERR (Toronto). Five papers bearing on subjects of urological interest were presented.

In giving an analysis of 140 consecutive cases of recurrent renal lithiasis Dr. J. BALFOUR (Vancouver) discussed the value of biochemical investigation in disclosing latent parathyroid disease. With the exception of 10 cases with metabolic calculi, the remainder had all had calcium-containing stones. Of these, 10% were found to be associated with hyperparathyroidism. While elevation of the serum calcium still provided the easiest means of detection, there were some in which the value remained normal. In these, the use of the phosphorus reabsorption test with estimation of the urinary calcium excretion was sometimes of differential significance. The effect of calcium infusion on the serum phosphorus level was also notably different in parathyroid disease, and this test could be used with advantage as a method of post-operative assessment. Turning to recurrent lithiasis in general, the speaker referred to recent studies of urinary citric acid excretion and the importance of this substance in preventing the precipitation of calcium-containing stones.

In reply to Mr. Jacobs, Dr. Balfour stated that the post-operative prognosis in cases of hyperparathyroidism appeared excellent and that none of his patients had subsequently formed further stones.

Classification of Testicular Tumours

Dr. R. C. B. PUGH (London) drew attention to the confusion which at present existed in the designation and classification of tumours of the testes. Ambiguous terms based on different conceptions of the clinical behaviour and pathological appearances were in frequent use and led to obvious difficulties in gauging the prognosis. Marked discrepancies were apparent in reports of the incidence of certain types of tumour, and these had recently stimulated the establishment of a testicular-tumour panel in Great Britain for the purpose of further investigations. A scheme of classification had now been agreed, and it was hoped that urologists would submit specimens and clinical information to the panel for assessment.

Percutaneous Needle Biopsy of the Kidney

In describing an extensive personal experience of the method, Dr. G. N. RANKING (Toronto) outlined the indications for renal biopsy and gave a brief description of the technique. It was possible to obtain tissue not only for histological examination, but also for bacteriological culture, and this had been useful in the differentiation of cases of pyelonephritis. Furthermore, the method might now have application in the differential diagnosis of renal cysts and tumours, in the assessment of patients for renal dialysis, and in post-operative studies after renal transplantation. The risks and inconveniences of the procedure were very slight.

Supervoltage X-ray Treatment of Bladder Tumours

Mr. D. BAND (Edinburgh) described the results of treatment by external supervoltage irradiation in a series of 87 tumours of the bladder, which had been followed for over three years. Among these were 9 cases of papilloma, 43 cases of papillary carcinoma, and 35 cases of solid carcinoma. The results in the intermediate group bore favourable comparison with those obtained by surgery, although perhaps the period of study was insufficient to allow a final opinion to be expressed. The palliative effect of supervoltage therapy in advanced cases of solid malignancy was also quite evident.

Sir ERIC RICHES (London) stressed the difficulties of subsequent operative procedures if they became necessary after standard methods of irradiation.

Prognosis of Genito-urinary Tuberculosis

Dr. G. L. GALE (Toronto) presented a report of 818 cases of genito-urinary tuberculosis which had been under the care of Dr. W. K. Kerr and himself at the Toronto Hospital for Tuberculosis. These were divided into 82 cases treated conservatively without either nephrectomy or chemotherapy, and followed for 20–35 years; 347 cases in which surgery had been carried out as indicated, but without chemotherapy, and observed for upwards of 15 years; and 389 cases treated by nephrectomy as indicated with the addition of chemotherapy and followed from 1½ to 11½ years. The mortality and morbidity statistics gave a clear indication of the immense importance of a prolonged chemotherapeutic regime, and, whereas in the earlier series 39% of the cases were dead within five years, not one of the recent series had succumbed to tuberculosis. The recommended regime comprised daily injections of streptomycin, 1 g., with 14 g. P.A.S., and 300 mg. isoniazid orally. In some cases the dose of isoniazid was raised to 600 mg. daily and supplemented by pyridoxine.

THE SCIENTIFIC EXHIBITION

The Scientific Exhibition held during the Joint Annual Meeting at Edinburgh was the best and biggest since these exhibitions started in 1952. The 83 separate displays were all of a high standard, although, as in previous years, space for the visiting crowds was at a premium.

A welcome development in the Exhibition over the last few years, and particularly evident this year, has been an increasing trend for separate departments—for instance, of surgery and medicine—to combine to present a more comprehensive picture of a method or of a disease than either could give alone. And more exhibitors are thoughtfully providing descriptive literature for visiting doctors to take away and read at leisure.

Appropriate to the occasion, pride of place, at Stand 1 of the Exhibition, was taken by the Canadian Diabetic Association, which displayed historic events and present research on diabetes and insulin as well as the activities of the association.

In weight of numbers surgical exhibits predominated, with urology very much to the fore. The topical interest in heart surgery was well attested by the many visitors examining the displays devoted to various aspects of this subject. General, orthopaedic, and paediatric surgery were also represented by excellent demonstrations from many parts of the United Kingdom. The other displays could be broadly grouped under "Medicine," "Obstetrics," "General Practice," "The Services," and "Methods of Investigation and Illustration."

The Prize-winning Exhibits

At a reception at B.M.A. Scottish House on July 23, Sir ARTHUR THOMSON expressed pleasure at the greater size and yet higher standard of the Exhibition, and the Association's gratitude to the exhibitors. Dr. E. ASHWORTH UNDERWOOD, the adjudicator, then announced the prize-winners. In the section in which merit was measured by the scientific value of the exhibit the winners were Mr. J. F. SIMPSON and Dr. P. N. CARDEW (St. Mary's Hospital Medical School, London) for their exhibit "Endoscopic Cinematography of the Larynx"; Dr. EDITH K. DAWSON and Professor D. E. C. MEKIE (Royal College of Surgeons of Edinburgh) for their

exhibit "A Study of Breast Pathology"; and Dr. F. R. PHILPS (University College Hospital Medical School, London, and St. Mary's Hospital, Eastbourne) for his exhibit "The Identification of Carcinoma Cells in the Sputum." Honourably mentioned in this section were Professor J. BRUCE, Dr. W. I. CARD, and their colleagues from the Gastro-intestinal Unit of the Western General Hospital, Edinburgh, for their exhibit "The Contribution of Hormone Therapy to the Management of Ulcerative Colitis"; Professor R. WALMSLEY (St. Salvator's College, University of St. Andrews, Anatomy Department) for his exhibit "Sections of Entire Thoraces, Illustrating Chambers of the Heart"; and Dr. R. C. B. PUGH, Dr. ELSIE N. K. WALLACE, and Mr. D. M. WALLACE (Testicular Tumour Panel and Registry, and Clinical Testicular Tumour Group) for their exhibit "Clinico-pathological Investigation of Testicular Tumours."

In the section where the teaching value of the exhibit was the criterion of merit there were again three prize-winning exhibits: Professor J. I. P. JAMES and Mr. J. CHALMERS (Department of Orthopaedics, University of Edinburgh) for their exhibit "The Fate of a Bone Graft"; Mr. J. A. ROSS (Edinburgh Royal Infirmary) for his exhibit "Anatomical Demonstration of Normal and Abnormal Human Kidneys"; and Mr. T. GRAHAME (Department of Veterinary Anatomy, Edinburgh University) for his exhibit on "The Kidney in the Animal World." Four exhibits in this section received honourable mention: Mr. ARTHUR H. JACOBS (Urological Department, Glasgow Royal Infirmary) for his exhibit "The Use of Intestine in Reconstructive Urinary Surgery"; Dr. G. W. SENTER (Walsall Group of Hospitals) for "The Third Dimension"; Dr. E. F. J. BROOKS, Mr. A. SMAILOWSKI, and Dr. D. J. CURRIE (Department of Photography, St. Michael's Hospital, Toronto) for their exhibit on "Photography in Medicine"; and Dr. J. MARSHALL and Dr. F. CLIFFORD ROSE (Institute of Neurology, London) for "The Carcinomatous Neuromyopathies."

THE HISTORICAL EXHIBITION

The famous and the notorious side by side—that was the piquant feature of the Historical Exhibition at the Museum at the Royal College of Surgeons of Edinburgh during the Joint Annual Meeting. The commemoration at the same time of two such contrasting characters as Charles Bell and William Burke was both enterprising and fascinating, and the care which had been taken in assembling the exhibits was well repaid by the enthusiastic interest of the visitors to the museum.

The amazing versatility of Sir Charles Bell was well attested by 141 exhibits. Anatomist and neurophysiologist, artist and sculptor, civilian and military surgeon, essayist and author, collector of anatomical and pathological specimens—all these aspects of his work were illustrated and exemplified.

The name of William Burke lives on as a verb—"to burke"—and the nefarious activities of Burke and Hare in providing material for the anatomists in Edinburgh at the beginning of the nineteenth century inspired at least three books and one play. Burke and Hare were not true "resurrectionists": they did not raise the already dead, but anticipated natural death in order to sell the bodies to Dr. Robert Knox. Hare turned King's evidence and escaped to Ireland. Knox fled to London, where he died in poverty. Burke was tried and hanged. And, of the twenty-one exhibits shown, the pocketbook made from his skin may have been the most gruesome, but the most enthralling was a page of *The Scotsman* of January 31, 1829. The descriptive columns entitled "The Execution of Burke" read as a masterpiece of writing of its kind and faithfully evoked the atmosphere of that public occasion. And the reader who looked further saw that the following article was entitled "Phrenological Observations on the Head of William Burke."

MEDICO-LEGAL SYMPOSIUM

Tuesday, July 21

A medico-legal symposium, arranged jointly by the Canadian Medical Protective Association and the British medical defence societies, was held at Adam House. Dr. GEORGE W. ARMSTRONG, president of the Canadian Medical Protective Association, took the chair, and introduced the following speakers: Dr. T. L. FISHER (secretary-treasurer, Canadian Medical Protective Association); Dr. J. H. B. HILTON (associate secretary-treasurer), Dr. ALISTAIR R. FRENCH (secretary, Medical Protection Society); Dr. PHILIP H. ADDISON (secretary, Medical Defence Union), and Mr. T. W. WOLSTENCROFT (solicitor to the Medical and Dental Defence Union of Scotland).

Medico-legal Problems of Anaesthesia

Dealing with the medico-legal problems of anaesthesia, Dr. ALISTAIR FRENCH said that anaesthetists practising modern techniques were exposed to increasing medico-legal risks. The experience of the Medical Protection Society was that the vast majority of complications arose from anoxia or anoxaemia, the cause of which might be mechanical obstruction to respiration, central paralysis of the respiratory function, or sheer oxygen starvation caused by some fault in the anaesthetic apparatus or error in turning on the right tap.

Local analgesia also had its hazards. There had been several cases where patients had died as the result of a large overdose of adrenaline, mistakenly given because there was an error in labelling the bottle or an error in reading the label by the surgeon and/or the nurse.

Sexual Sterilization

It was difficult to know why so many people desired or were willing to be sterilized when there was no sound medical reason for it, said Dr. T. L. FISHER. It was no less puzzling why so many doctors allowed themselves to be persuaded to commit that assault on their patients' persons, and it was still less comprehensible why so many doctors, apparently, suggested it.

The problem was straightforward. Should sexual sterilization be done when it was not necessary medically? But the guises in which the problem appeared were many. The commonest seemed to be a sickly wife, but it was seldom a sickly wife who wished to be sterilized. It was the husband who feared for his wife's health. Doctors often contributed to the confusion by advising women that they should have no more children.

Under British law the problem of sexual sterilization was susceptible of fairly easy solution. There might be places where specific laws allowed sterilization for named reasons, otherwise sexual sterilization was legal only when it was an integral part of some procedure itself necessary for the preservation of the health or life of the individual who was to be sterilized. That allowed, for example, for the incidental sterilization of a women with uterine fibroids. It allowed for the sterilization of a woman who, for any valid medical reason, should not have children, but, it must be noted, it did not allow, for her protection, for the sterilization of her husband, to whom pregnancy was no personal menace.

Parental Consent

Dr. PHILIP ADDISON chose as his subject "Consent to Operations, etc., in the Case of Patients aged between 16 and 21." Although, he said, there could be little doubt that, except in an emergency, consent must be obtained from the parent or guardian for treatment of a person under 16 years of age, there appeared to be no direct authority in the United Kingdom upon whether the consent of a minor who was aged between 16 and 21 was sufficient, and it was

therefore necessary to treat the matter as one of principle. As a person who had attained the age of 16 could, generally speaking, live where he liked and away from the control of his parents, it would seem that a sharp distinction must be drawn between minors who had and those who had not attained the age of 16 years. A practitioner would, in Dr. Addison's view, be most unwise to assume that the consent of the parent or guardian of a patient of the age of 16 or over and of normal intelligence was equivalent to the consent of the patient. He suggested therefore that, in considering the age at which consent could be said to be true and valid, it would be safe to follow the lead given in the legislature relating to sexual conduct and mental illness, and that no attempt should be made to obtain the consent of any minor under 16 years of age.

Mislaid Foreign Bodies

Dr. J. H. B. HILTON said that, although all surgeons must be aware that foreign bodies could be left behind at operations, a number of them at least seemed to feel that that sort of thing could never happen to them. To try to bring home to the medical profession the danger of such accidents occurring, the Canadian Medical Protective Association had continued to send articles to the *Canadian Medical Association Journal* pointing out the dangers, and illustrating the problem with pertinent case histories. Aside, however, from keeping the profession alive to the need for continuous care, there were other things which could be done to help prevent such accidents. Sponge counts were useless unless carried out scrupulously: the count when completed should be recorded and signed and the document should be made part of the case-history chart and of the operation record. Close co-operation between the surgeons and the operating-room staff must be obtained to make instrument counts feasible. Laparotomy and gauze sponges should have a radio-opaque tag so that they could be recognized by *x*-ray should they be left. When there was any doubt about a sponge count, even after a careful search, the abdomen should be closed, and within the next twenty-four hours an *x*-ray film should be taken. If the laparotomy pads and sponges had radio-opaque markers and the *x*-ray showed nothing, it could be felt that every precaution had been taken.

Medical Negligence

"Unless there has been negligence, a claim for compensation against a doctor cannot succeed," said Mr. WOLSTENCROFT, solicitor to the Medical and Dental Defence Union of Scotland. A large proportion of the cases against doctors alleged that the doctor did something wrong and was negligent, and so caused injury. In Scotland it had been laid down authoritatively that, to establish liability by a doctor in a case where deviation from normal practice was alleged, three facts must be established. First, it must be proved that there was a usual and normal practice, and just what that practice was. Secondly, it must be proved that the doctor did not adopt that practice. Thirdly, it must be established that what the doctor did was something which no doctor of ordinary skill would have done if he had been acting with ordinary care.

New Zealand research workers investigating Polynesian blood groups in Auckland hope to find factors which may give a clue to the direction of the prehistoric migrations of these people in the Pacific. The investigation is being conducted at the Auckland Hospital Laboratories under the auspices of the Auckland Medical Research Foundation. It will be extended to include the Samoans and Tongans, and later probably the people of the Society Islands, Tuamotu, and the Gilbert and Ellice groups (*Forefront*, New Zealand Monthly Survey, September, 1959).

SECOND WORLD CONFERENCE ON MEDICAL EDUCATION

CHICAGO, AUGUST 30–SEPTEMBER 4

[FROM A SPECIAL CORRESPONDENT]

In our Educational Number, on September 5, we printed Dr. Raymond Allen's presidential address to the Second World Conference on Medical Education, the reports to the Conference by Professors Melville Arnott and Ian Aird on, respectively, the "Proceedings," and the "Conclusions and Results" of the First World Conference, and the five opening papers given on the first afternoon of the Second Conference. Three of these dealt with international co-operation in postgraduate medical education, and the other two with the educational value of research. Below we print an account from a Special Correspondent of the rest of the Proceedings of the Second World Conference.

Opening Plenary Sessions

Like most international conferences, the Second World Conference on Medical Education, which was held in the Palmer House Hotel, Chicago, from August 30 to September 4, raised more questions than it could provide the answers for. It was a slightly bigger conference than its predecessor, held in London in 1953, for nearly 800 medical educators put in an appearance there. Of this number, at least half came from the United States, with the second biggest delegation a Canadian one, and the United Kingdom in third place. Other nations well represented were Germany and India, but altogether some 67 countries had found someone to represent them.

The pattern of the conference followed that of the first one, with plenary sessions on the Monday and Friday, and four concurrent Sectional meetings on the intervening three days. The president of the conference was Dr. RAYMOND ALLEN, who has just left a vice-chancellorship at the University of California to become the head of the United States International Co-operation Mission to Indonesia. He was ably supported by two vice-presidents, Dr. R. FARQUHARSON, professor of medicine, University of Toronto, and Dr. VICTOR JOHNSON, director of the Mayo Foundation for Medical Education and Research. Each Section was provided with two vice-presidents, the United Kingdom being represented by Sir GEORGE PICKERING, regius professor of medicine, Oxford. The Monday plenary session began with addresses of welcome from representatives of the sponsoring organizations, such as the president of the World Medical Association, Dr. C. JACOBSEN, of Denmark, the director general of the World Health Organization, Dr. M. CANDAU, and representatives of the Council for International Organizations of Medical Sciences, the International Association of Universities, the American Medical Association, and the Association of American Medical Colleges. Then came Dr. RAYMOND ALLEN'S presidential address and the other opening papers, which were published in the *Journal* earlier this month (September 5, pp. 319–336). These will not be repeated here.

In the discussion on the five afternoon papers, Dr. A. BEAUCHAMP (United Kingdom) chided the speakers for their concentration on the technical side of postgraduate education, which he felt should include readings in philosophy and the best of the authors in the physician's own language.

Basic Clinical Training for All Doctors

After three days of Sectional meetings, Friday morning produced the long-awaited reports on the deliberations of these Sections. It became apparent from these that much overlapping had taken place in the discussions of the various sections, and also that the main concern of participants had been with the postgraduate education of the general practitioner. It was also apparent that everyone was more

or less satisfied with the present programme for training specialists, but no one was satisfied with the programmes for general practitioners.

Professor E. HUGH LUCKEY, of Cornell Medical College, summarized the discussions of Section I on basic clinical training for all doctors. He indicated that the finding that the curriculum for medical students should provide a balanced base for any further lifelong study meant compromise between the various claimants on the students' time. The learning methods should not hinder the brilliant student and should give the maximum help to the poor student. Emphasis should be on small group and bedside teaching, and sound methods of observation of patients should be developed. The integration of specialties into the general curriculum was very difficult, and it might be necessary to institute polyclinical services in which care was given by a team of specialists and general physicians as required. Nobody seemed to have found the right formula for integrating social sciences into the medical curriculum. Professor Luckey discussed the advantages and disadvantages of extramural clinical preceptorship, giving as his personal view the belief that the reasons advanced for this type of training were not really valid. The two vice-presidents of the Section discussed the difficulties of integrating social medicine and the specialties into the curriculum.

Advanced Education for General and Specialty Practice

Section II had been given the task of discussing advanced training for general and specialty practice; their findings were summarized by Professor OLIVER COPE, of Harvard Medical School. He said that speakers had plunged bravely into both topics, but the swimming was rough. There was general dissatisfaction with the general practitioner and not even agreement on his scope or definition. Professor Cope thought that the general practitioner's job was at present a difficult one and indeed almost impossible. Dissatisfaction with general practice was due to the fact that the practitioner's knowledge was less than first-rate because of the large number of subjects involved, and the fact that he was forced to practise at a sub-standard level compared with the specialist and therefore immediately assigned a second-class position in the medical hierarchy.

Much had been made of the care of patients with emotional disturbances in general practice, but this required more time than the general practitioner had available. In fact, the job was basically unsatisfactory for intelligent students seeking interesting work, and the remedy was not, in Professor Cope's opinion, to dilute the curriculum by introducing general practitioners as teachers—a suggestion which had been made by some participants. The ultimate solution might lie in group practice, with the specialist in internal medicine becoming the family doctor. This would take time, because doctors were essentially individualists. In any case it was first necessary to know what kind of general practitioner one wished to produce before formulating his educational programme.

In this Section the discussion on specialty education had run much more smoothly, with general agreement on the need for residency programmes. Professor Cope then castigated the almost fanatical rush of United States doctors to become very narrow specialists. This had killed the sense of unity in American medicine, which was approaching a state of anarchy. The fault lay with the clinical practitioner and not with the medical faculties. In further discussion of the work of this Section, Sir GEORGE PICKERING referred particularly to internships, pointing out that many students had to obtain these in second- or third-rate hospitals. He felt that the latter should provide as a minimum good-quality staff, post-mortem examinations, library facilities, at least one weekly staff discussion, and time for the young doctor to read in the library. The specialist should also spend some time in a wide specialty before narrowing his interests, and in addition have some extra training in basic sciences. He thought that there should not be too many examinations, which otherwise tended to hinder self-education. It was probably desirable for the State not to intervene in postgraduate education, but to leave this to the universities and the professional associations.

Development of Teachers and Investigators

Section III had discussed the development of teachers and investigators, and its work was summarized by Dr. T. B. TURNER, dean of the Johns Hopkins University School of Medicine. He said that the title of the Section suggested that the two callings were allied and that great investigators were necessarily great teachers and vice versa. He listed the three qualifications of the good teacher as: ability to convey knowledge, postgraduate attainment, and a capacity for original work. He pointed out the very small number of the medical profession who were actually carrying the burden of teaching or of research, and said that the responsibility for developing teachers and investigators rested with the medical faculty. Good teachers were attracted by the opportunity to teach good students, and the influence of teachers was powerful and decisive. Some thought should be given to teaching teachers how to teach. Four ideas had recurred in discussions: (1) that the teacher must be an investigator; (2) that the investigator must be a teacher; (3) that the teacher-investigator should be found early and helped to develop; (4) that the superior teacher-investigator must be a citizen of the world.

Continuing Medical Education

The efforts of Section IV on continuing medical education were described by Dr. S. B. GILDER (Canada), who said that the Section had expressed some dismay at the amount of time spent on discussing purely technical training to the exclusion of education in the broadest sense, which included a wide acquaintance with the humanities and the newer social sciences. As in other Sections, speakers had all been concerned at the relatively unsatisfactory state of education of the family doctor. Figures from several countries suggested that only about 10% of general practitioners were able to take advantage of the post-graduate instruction available to them. Overwork and financial barriers were the chief obstacles to their wider education, and speakers had advocated such measures as tax relief for education expenses, creation of fellowships and grants, efforts to cheapen production and distribution of textbooks and journals, and provision of locums for doctors attending courses. If the general practitioner was to be induced to take his responsibilities for continued education seriously, his teachers must impress on him from the beginning of his medical-student career that he was embarking on a lifelong pursuit of knowledge.

In countries with a mixture of insurance and private practice, postgraduate educational programmes must be developed voluntarily, or they might well be forced upon the profession by the State or other organizations. It might be thought that creation of more opportunities for voluntary postgraduate study would increase the number of persons involved, but it seemed that the same small proportion of practitioners took advantage of all the opportunities. One prominent point often overlooked was that the most important technique of postgraduate education was by contact with colleagues. This was an expensive method, but discussion of one isolated practitioner's errors and difficulties by a colleague, or the teaching contained in a carefully drafted hospital report on a discharged patient, could be invaluable. Nothing quite took the place of personal contact, and the character of the teacher was a key factor in success or failure of postgraduate programmes. Great emphasis was laid by section speakers on clinical teaching; social sciences, for example, had to be introduced as an adjunct to actual clinical discussions.

The speakers in this Section were by no means unanimous in their opinions on the educational value of research. One speaker had discussed the value of reading

in education, and said that general practitioners in Germany estimated that 70% of their education was obtained through reading and only 30% through audio-visual methods, though they would have liked to see these two figures reversed. Finding suitable authors for good educational articles was very difficult, and efforts had been made to bring together authors, editors, practitioners, and teachers. The speaker and also one of the vice-presidents of the Section discussed the demonstration of audio-visual communication techniques which had been arranged by Mr. RALPH CREER, of the American Medical Association, on Wednesday afternoon. This demonstration included discussion and demonstration of tape-recording techniques, sound-film techniques, two-way closed-circuit radio communication, and plain and colour television.

Speakers emphasized the need for adapting programmes in postgraduate education to the local conditions, and for a preliminary survey of the local situation before starting a programme. These programmes ought to include visits of practitioners from the periphery to medical centres, and also visits to the periphery by specialists, who by this means would benefit as well as the general practitioners. The Section laid primary responsibility for postgraduate education on the universities; it felt that the university's medical faculty had no more right to disclaim responsibility for its students on graduation than a doctor had to wash his hands of a patient after he had discharged him. The faculty ought to act in liaison with professional associations who could help to put the academic staff in touch with the practising physician. Examples were given from several countries of the acceptance of funds from commercial sources for postgraduate education, and it was considered perfectly proper to use this money provided it was given unconditionally.

A panel of speakers agreed that it was very difficult to assess the results of postgraduate educational programmes, which were usually judged on two criteria: their popularity in terms of numbers attending, and the subjective satisfaction felt by participants. This, however, took no account of the long-term results, and investigations in the United Kingdom had suggested that general practitioners did not know what they wanted in the way of postgraduate education, and that what they wanted might not be what they needed.

G.P. Still the Backbone

The whole conference was then briefly summarized by Dr. WARD DARLEY, executive director of the Association of American Medical Colleges, who was of course only able to give his own impressions of the vast programme involved. Finally, the conference was given a rousing finish by the veteran medical statesman, Sir ARCOT MUDALIAR, Vice-Chancellor of the University of Madras, who in a half-hour oration said that medical education was a field in which there could be no rivalry, no jealousy, and no secrecy. He commented on his fifty years as an obstetrician, and regretted the absence at the conference of reference to the ancillary professions, such as nursing, public health engineering, and so on. He deplored some aspects of modern research, saying that the search for antibiotics resembled a gold-rush rather than a properly conducted scientific inquiry. He still felt that the general practitioner was the backbone of the profession, and said that specialism could not exist without him. Because of this the specialist had the responsibility of arranging postgraduate education for his general-practitioner colleagues. He thought that the standard of general practice was an accurate barometer for recording the state of the medical profession in any country.

The *Acta* of the first Afro-Asian Congress of Ophthalmology have been published by the Ophthalmological Society of Egypt, 42, Kasr-el-Ainy Street, Cairo. The volume (pp. 734+lxxii) contains the text of the 70 papers, the discussions, and other material concerning the congress, which took place in Cairo on March 1–5, 1958.

New Appliances

AIR-BED TO ASSIST THE TURNING OF PATIENTS

Dr. E. A. COOPER, of the Department of Anaesthetics, the Medical School, King's College, Newcastle upon Tyne, writes: An important principle in nursing and medical care is frequent turning of the patient from side to side. This applies especially to the weak or paralysed and to those suffering from pulmonary infection or respiratory paralysis. It is often impossible owing to lack of nursing help. This paper describes the development and use of a simple device which enables any nurse, single-handed, fully to turn in bed an unconscious or debilitated patient, the entire manœuvre taking only a few seconds. The device also enables many patients, otherwise too weak to do so, to turn themselves unaided.

The basic principle is as follows. If a patient lies on two long narrow air-cushions, one on either side of his vertebral column, he will tend to be turned away from the one which contains more air (Fig. 1 a). If the air is slowly

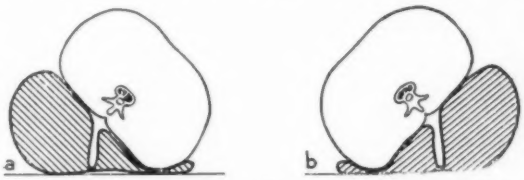

FIG. 1.—Two diagrams representing a patient lying on two air-cushions (shaded). In (*a*) the left-hand cushion is much fuller than the right. In (*b*) most of the air has been transferred from the left-hand to the right-hand cushion.

transferred from the more-inflated to the less-inflated cushion, he will be turned to his other side (Fig. 1 b). If the two cushions are equal and are symmetrically arranged on each side of the patient only the most gentle pressure is necessary to drive the air from one to the other. Such pressure can easily be applied by the transference of the weight of the patient's limbs from one side of his body to the other.

The device was originally conceived as an aid to nursing, but it was hoped that by making the act of turning more easy it would also be less distressing to the very ill patient. Experience has, however, shown almost universal gratitude among the patients for the comfort conferred not only in turning but throughout the rest of the day.

Description

The device is shown diagrammatically, with its dimensions, in Fig. 2. It is made by welding together two sheets of p.v.c., 0.02 in. (0.51 mm.) thick. A and B are two identical sausage-shaped sacs joined together by a wide tube, C. The length is such that in use, with the patient's vertebral column in the midline, the occiput lies within the curvature of C and the lower ends of the sacs extend to the mid-thigh. The system ABC represents the original device. However, it was possible for the patient to move appreciably from its midline (thus impairing its efficiency), and one patient complained that he felt himself to be too near the edge of the bed. In subsequent models, therefore, the two additional cushions, D and E, were incorporated. They are welded in the same sheet of p.v.c., but are pneumatically quite separate. In use, they are firmly inflated, and remain so regardless of the position of the patient, who then lies in a shallow pneumatic cot, and is given security against falling out of bed or moving from the midline. The complete device covers a standard mattress from side to side and is held in position by lateral flaps of p.v.c., which can be tucked

underneath. Each pneumatic system has its own p.v.c. tube for filling, ¼ in. (6.35 mm.) in diameter.

In practice the device is used in the bed between the ordinary mattress and the bottom sheet. When deflated it can be simply introduced like a drawsheet by two nurses while the patient is in bed. When in position, the ABC complex is approximately half inflated—that is, until one

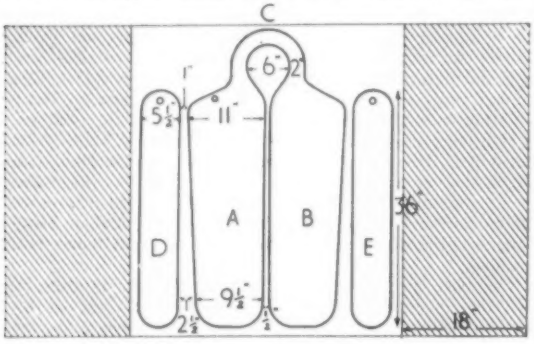

FIG. 2.—The device shown diagrammatically. A and B are the two large pneumatic cushions connected by the tube C. D and E are separate cushions. The shaded areas represent the lateral flaps for tucking under the mattress.

sac is fairly full and the other contains some air, but not enough to lift the patient off the bed. This usually takes 30–50 l., and can be done by a small bellows or pump, or by mouth. D and E are then filled to tautness, requiring about 10 l. each. The air is trapped in each of the three systems by folding the p.v.c. inlet tube on itself and fastening it by an ordinary screw clip as from a drip set. The flaps are then tucked in and the rest of the bed is made, the whole procedure taking 10 to 15 minutes.

It is important to appreciate the principle on which the device is based. The idea is not that the patient should be completely separated from the mattress by a layer of air, but that the large volume of air should be under only one side of him, thus keeping him turned towards the other. Actually there is some air underneath the side of the body on which he is lying, and this does ensure more even distribution of pressure and makes for greater comfort; but it is an incidental rather than the main feature of the device. The position of the patient depends on the weight and position of his limbs. Thus if a weak or paralysed patient can move one or two limbs sufficiently he can alter the relative pressures in the two sacs and drive the air to the other side, and his body will then turn after his limbs. Similarly, a nurse wishing to turn an unconscious patient can move the limbs and, with or without slight pressure on the inflated sac, turn the entire patient in one movement and stabilize him on the other side. It also follows that, as the central compartment is only partially inflated, the device is much more effective for the lying than for the sitting or semirecumbent patient.

Practical Experience

The use of the air-bed device for the first 50 patients is described below. All could be turned satisfactorily by one person: 15 could not turn themselves from side to side on an ordinary hospital bed, but with the help of an air-bed 10 were enabled to do so. Of the other five, only two had any muscular power in any limb. No patient developed a pressure sore who had been free when first put on the air-bed.

Thirty-two of the patients were nursed on an air-bed for longer than one week (23 for less than four weeks, 9 for more). The longest period was 15 weeks. 13 patients (9 of whom were completely immobile) were free of pressure sores initially and remained so throughout. One of these, on withdrawal of the device after many weeks, developed a sore on the fourth day. The air-bed was replaced and the sore healed in the second week. The other 19 patients had sores of all degrees of severity when first put on air-beds. Of these, 10 healed completely, 5 improved, and 4 remained stationary or deteriorated. All these patients had their pressure areas treated on established routine lines.

All but two of the patients capable of expressing an opinion welcomed the device. The two who did not like it had both undergone laminectomy on the previous day. One preferred to turn via the prone position. The other was anxious lest he fell out of bed, and it was after this that the side cushions were added. In fact, no patient has ever fallen out of bed when one of the devices was in use. The nursing staff have considered the air-bed excellent in over half the cases and useful in all the others. Its use has never been abandoned unless the patient was discharged or died, or the pressure sore had healed. The treatment of pressure areas is facilitated because the inflated cushion under the patient's upper side can be depressed locally by one hand while the other applies the treatment. The patient is then turned and the other side treated. It is also satisfactory that the softly inflated cushions do not interfere with the use of bedpans.

The air-beds have proved reliable in use. Seven of the final model have been in continuous use for five months, during which time, of the 21 air compartments at risk, only two have leaked (one central and one lateral). Both leaks were due to faulty welding and were readily repaired. Once inflated, the beds did not require frequent topping up. One was used for 15 weeks without interference.

The devices have also been used in tank respirators, and, when inflated more firmly, as back-rests and leg-rests.

I am grateful to Professor E. A. Pask for his help and encouragement during the development of this air-bed. It is understood that Messrs. J. C. Peacock and Son Ltd., 22–28, Collingwood Street, Newcastle upon Tyne, 1, may be willing to manufacture the device on request.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Megimide (Aspro-Nicholas).—This has the approved name bemegride and chemically is β,β-ethyl-methyl glutarimide. It has a structure (Fig. 1) similar to the basic structure of the barbiturates (Fig. 2).

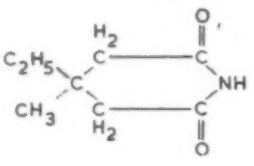

FIG. 1

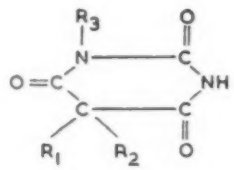

FIG. 2

Bemegride has a direct stimulant action on the central nervous system. It probably stimulates particularly the reticular nuclei of the brain stem, facilitating transmission through the reticulocortical and reticulospinal systems.

In normal subjects small doses increase the pulmonary ventilation and reflex responses and also cause changes in cerebral electrical activity. Similar doses given to epileptic patients, or larger doses to normal subjects, produce seizure discharges in the electroencephalogram, and actual convulsions if the doses are increased. When given to patients suffering from barbiturate poisoning bemegride accelerates recovery of respiratory functions, corneal reflexes, and oropharyngeal and somatic reflexes. It accelerates the electroencephalogram and diminishes the depth of unconsciousness. As in the normal subject, increasing dose of bemegride in these patients produces seizure discharges in the electroencephalogram and eventually may cause

convulsions. The electroencephalogram changes can be reversed and the convulsions stopped by the intravenous administration of sodium thiopentone.

Although at first it was thought that bemegride had a specific action in antagonizing the depressant effects of barbiturates on the central nervous system, this view is now no longer held. Bemegride is looked upon as a non-specific stimulant of the central nervous system and beneficial in treating cases of poisoning by various other narcotics (other than barbiturates), such as primidone and glutethimide, as well as barbiturates.

Therapeutic uses of bemegride are as follows:

(1) In the treatment of acute barbiturate poisoning. Here, in addition to the usual general method of dealing with a comatose patient, a 5% glucose saline intravenous infusion is given slowly, and 10 ml. of 0.5% solution of bemegride (50 mg.) is injected into the tubing leading to the intravenous cannula every three to five minutes. Some clinicians precede each injection with 1 ml. of a 1.5% solution of amiphenazole (15 mg.). The bemegride (and amiphenazole if used) is continued until the "safe state" is reached—that is, return of all reflexes, including coughing and swallowing reflexes—and the patient shows signs of spontaneous movements, though they are still unconscious. Administration is discontinued before the patient actually awakens in order to reduce the possibility of producing any side-effects of the drug. Up to 2,000 mg. bemegride (and 600 mg. amiphenazole) can be given in two hours with safety. If the "safe state" is reached before this amount is given, then the drug is discontinued. Usually the patient recovers from the "safe state" spontaneously without further treatment, but occasionally in poisoning with the longer-acting barbiturates regression may occur—that is, the patient gradually sinks back into a deeper state of unconsciousness. Then further courses of treatment can be repeated, usually at intervals of 6 to 12 hours, until eventually the patient does recover. Another method of administering the bemegride is by means of a continuous intravenous drip of 100 ml. normal saline containing 500 mg. bemegride (and 150 mg. amiphenazole if wanted) over a period of 30 minutes, and repeating this as required.

Side-effects of bemegride which may occur with this treatment are vomiting, convulsions, and delirium. The danger of vomiting is the aspiration of stomach contents, with consequent pulmonary complications. The patient is usually in the "safe state" by this time and the drug is discontinued. Occasionally finger-twitchings occur, and they are an indication to reduce the dosage or rate of administration of the drug or discontinue administration to avoid the possibility of convulsions, which may, though rarely, follow. If convulsions do occur a small intravenous injection of 2.5% sodium thiopentone will rapidly eliminate them. At any time from recovering consciousness up to four days later the patient may suffer mental disturbances. They take the form of restlessness, visual and auditory hallucinations, delusions, and occasionally epileptiform convulsions. Paraldehyde will usually help to control them. These disturbances, which are benign and leave no permanent after-effects, seem to occur most frequently in patients who have previously become habituated to barbiturates or in patients who have been given too much bemegride and who may have shown side-effects during the course of treatment.

(2) In the treatment of acute poisoning by primidone and glutethimide, bemegride is given in the same way (sometimes with amiphenazole) as in acute barbiturate poisoning.

(3) It may be used for the termination of surgical anaesthesia for which barbiturates have been used. Here 50 mg. is usually injected intravenously.

(4) It may be used as an activating agent of the electro-encephalogram, for diagnostic purposes, to produce in epileptiform patients the characteristic spikes in the E.E.G. without inducing convulsions.

N.H.S. Basic Price.—Injection, 0.5% w/v, 6×10 ml. 20s.; 6×30 ml., 36s.

"It is profoundly regrettable that in 1958 there were 300,000 persons killed or injured on the roads in Great Britain. Deaths rose from 5,590 to 5,970. This is the worst toll for any year so far. There was an increase among all classes of road users except for a small reduction among riders of motor-assisted pedal cycles. A record number of 50,000 children were killed or injured; 10,000 of these child victims were passengers in vehicles" (*30th Annual Report, 1958.* Pedestrians' Association for Road Safety).

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Isaac Wolfson Foundation's Fund

SIR,—I would like to thank you for your leading article on the subject of the recent magnificent grant to the Royal College of Physicians (*Journal,* September 12, p. 416) and for giving space to a description of the important activities of the Isaac Wolfson Foundation (p. 427). This grant is indeed a historic gift which my College and British Medicine are not likely to forget.

What is not quite so obvious is that it will be also a historic gift to British architecture. In these utilitarian times opportunities for the design and erection of fine buildings are all too few. We look forward to a building worthy of the College, worthy of its setting in Regent's Park, and at the same time a fitting monument to the generosity of the benefactors.—I am, etc.,

London, S.W.1. ROBERT PLATT.

Risks of Immunization

SIR,—Apart from its special merits, Dr. E. R. Hargreaves's interesting letter (*Journal,* September 5, p. 367) reflects a widespread concern and the need for authoritative guidance on all immunizations.

There have been endless variations on the same theme published in the *Journal* during the last two years, and many of them offer conflicting advice. Allowing for special considerations affecting individual cases, there must surely be enough scientific evidence and practice experience available by now to make it possible for the Ministry to give a lead by issuing a sound authoritative "guide" which would enable all doctors to speak with the same voice on these matters. The success of immunization programmes in the prevention of disease depends as much on public confidence in the measures advocated as on their efficacy and safety. The present bewildering diversity of opinion in the profession as to the order and age of administration of the various vaccines does nothing to inspire confidence. On the contrary it tends to encourage fears and doubts in the lay mind—not to mention in some professional minds too.—I am, etc.,

Blakeney, Norfolk. W. H. CRICHTON.

SIR,—In discussing the risks of smallpox vaccination we might profitably start by asking why should we vaccinate babies at all. We cannot pretend that we do so in order to protect the infant from an imminent danger. The age distribution of notified cases in this country over the last decade shows that small children are less exposed to risk than other age groups. Taking the five-year period chosen by Dr. E. R. Hargreaves, for example (1953–7) (*Journal,* September 5, p. 367), there was only one case of smallpox notified in England and Wales in the age group 0–5 years though there were between 2½ and 3 million unvaccinated small children continuously at risk.

For many years it has been established British teaching that we vaccinate babies in order to reduce the incidence of complications if the procedure has to be repeated in later life. The assumption on which this

teaching is based—namely, that the safest age for primary vaccination is infancy—may well have been correct at some time in the past. It is now, however, demonstrably false. The figures reported to the Wellcome Foundation Symposium (see *Journal*, May 23, p. 1342), based on the experience of the greater part of the United Kingdom for the years 1951–7, give the following rates of incidence and mortality per million primary vaccinations:

Complications of Primary Vaccination (per million procedures)

	Age Group	
	0–1 Year	1–5 Years
Incidence:		
Generalized vaccinia	51·0	23·1
Post-vaccinal encephalitis	15·8	2·1
Total	66·8	25·2
Mortality:		
Generalized vaccinia	5·1	Nil
Post-vaccinal encephalitis	8·7	,,
Other complications	2·0	,,
Total	15·8	,,

As Dr. Hargreaves points out, the diagnosis in many of the cases and deaths in infancy is open to question. In some of the confirmed cases it could be argued that vaccination only served to administer the *coup-de-grâce* to infants fated to die young in any event because of agammaglobulinaemia. Nevertheless, in the face of these figures it can no longer be contended that infancy is the safest age for primary vaccination. The period 1–5 years is certainly as safe and probably safer. Bearing in mind the crowded schedule of immunizations recommended in the first year of life—against pertussis, diphtheria, poliomyelitis, tetanus, and perhaps tuberculosis—there is surely something to be said for postponing smallpox vaccination to a later period. The recommendations of the Symposium, therefore, allowed for smallpox vaccination to be performed at any convenient time in the first five years (not necessarily in the period 1–5 years as stated by Dr. Hargreaves) at the physician's discretion, thereby recognizing that the bogy of the enhanced risk attaching to vaccination after the first few months of life had been laid.

Statistical considerations are obviously not the only ones that need to be taken into account. Under present-day British conditions, however, it might prove that primary vaccination on school entry would ensure a higher acceptance rate and a lower risk of complications. This might well be combined with revaccination of school leavers to ensure a high level of herd immunity—a state of affairs which we certainly are not achieving at present with the emphasis on infant vaccination.—I am, etc.,

Anglesey. G. WYNNE GRIFFITH.

Quarantine Outmoded

SIR,—I have only just seen Sir George Pickering's letter on this subject (*Journal*, August 29, p. 305). In regard to the majority of the school epidemic decrease I agree with him wholeheartedly. Rubella, however, seems to me a very special case.

It is not clear from his letter what type of school his daughter attends—wholly boarding; part boarding and part day school; or wholly day school. If wholly boarding, I entirely agree with him—of course there should be no quarantine. But in the case of German measles young married teachers should be warned of the great risk they run in early pregnancy, and should, if in this state, be advised to stay away. In a mixed boarding and day school the problem is much more difficult. The boarders become a central nidus in which risk of gross infection in dining-hall and dormitory is raised so that there is an increased risk causing a pandemic in the day children. Many of these are using public transport, and, in my view, they should be told of the danger to young mothers and use their intelligence as to where and how they travel and should avoid cinemas, etc., during the "quarantine" period. Parents should receive a helpful and explanatory letter about the subject. In a wholly day school, "quarantine" should be observed in the same way.

Surely a policy of laissez-faire, which Sir George Pickering appears to advocate, is hardly applicable to a problem so serious; to a disease for which, if contracted in early pregnancy, many experienced obstetricians advise termination.—I am, etc.,

Northwood, Middlesex. DUDLEY M. BAKER.

Inoculation Recording by Tattooing

SIR,—Mr. Norman Lake (*Journal*, August 8, p. 141) is to be congratulated on his suggestion of permanent recording of inoculation by tattooing. Now that Dr. A. J. Rowe (*Journal*, September 12, p. 433) has shown that an instrument already in production, the Heaf gun, is suitable for the actual tattooing it is to be hoped that this will be taken up on a national or even on an international scale.

Tetanus toxoid is the only inoculation for which permanent recording is necessary, but in addition to the simple "T" the date of expiry of immunity should also be recorded. For that reason the site chosen must be visible to the patient himself so that it will remind him to receive another injection of tetanus toxoid, after which another date would be added. A case can also be made for similar recording of blood grouping. The patients in whom it is found that special care is required in cross-matching can have a red asterisk added after the blood grouping. Thus the patient in Group O Rh-negative would be tattooed O N. The patient in Group O Rh-negative who already had antibodies present would be tattooed O N*.—I am, etc.,

Banbridge. H. W. GALLAGHER.

Incidence of Intussusception

SIR,—I was very interested to read the article by Professor Donald Court and Dr. George Knox on the incidence of intussusception in the Newcastle children (*Journal*, September 12, p. 408). During my first post as house-surgeon at the Hospital for Sick Children, Newcastle, before the 1939–45 war we did not consider it an unusual event to operate on infants for intussusception. It wasn't till I began working in Leicester and later in London that I realized that it was a much less common event in the south of England.

In the years preceding the war contributory factors in the causation of intussusception were thought to be: (*a*) Unwise additions to the diet during the early weaning period. Offering the infant "a little of what he fancies" on the assumption that it would do him good. Such things as "jellied eel" often fell into this category. (*b*) The presence of mesenteric glands.

Before the war there was a great deal of unemployment in Northumberland with a consequent low standard of living. Tuberculosis among children was

not uncommon in those days. To-day, with the presence of the better supervision of children's feeding habits and the much better standard of living, these two causes should no longer play a great part. It is therefore surprising to find that the figures are still so much higher in Newcastle than in the Midlands and south of England.—I am, etc.,

West Kent General Hospital, Maidstone. SILVIA W. PYDDOKE.

Treatment of Pilonidal Sinus

SIR,—I was most interested in the article by Mr. A. J. H. Rains (*Journal*, August 15, p. 171). I am firmly of the opinion that in view of the long convalescent period required it is undesirable to perform excision of a pilonidal sinus and allow the wound to heal by second intention. I am equally diffident, however, about primary suture of the wound at least as far as the deeper structures are concerned. It seems to me a departure from a major surgical principle to use deep sutures of catgut in an infected, or at any rate potentially infected, wound.

In my own practice I have overcome this difficulty of deep suturing by applying the principle of negative-pressure drainage. The sinus is excised in the usual way, after the injection of indigocarmine into the primary opening, and as much skin as possible is preserved. The skin is sutured with interrupted silkworm-gut sutures and a plastic "portex" tube, the lumen of which is about 1 cm. in diameter, is introduced about 3 cm. from the lower end of the wound. About 4 cm. of tube lies within the wound and two side-holes are cut in it. Preliminary suction is started in the theatre as soon as the wound has been closed and made air-tight, and the tube is connected to the ward electric suction machine when the patient returns there. Haemostasis is secured in the usual way before the wound is sutured, but the negative-pressure drainage eliminates any dead-space in the wound by closely applying the skin flaps to the underlying structures. Suction is continued for five days, when the tube is removed. The skin sutures are usually removed on the tenth post-operative day. I have not noticed any increased liability to sepsis after this type of operation, and the convalescent period is remarkably short compared with the results of healing by second intention. In a short series of cases operated upon over the past three years there has not so far been a recurrence using this method.—I am, etc.,

Northampton. DEREK LAMBLEY.

SIR,—I have been reading with considerable interest the recent letters (*Journal*, September 12, p. 430) that have appeared on the above subject. One well remembers the prolonged incapacity which "jeep disease" used to engender in the war years, when vast excisions were allowed to granulate slowly up, like the perineal end of an abdomino-perineal in the "bad old days." Primary closure and anchor dressings revolutionized the treatment, and this has been the treatment that I have adopted since the war, in company, I think, with the majority of surgeons. I have, however, noticed that where patients have a sedentary occupation pain in the sacral area is often a late and a prolonged complication.

I have always felt a little unhappy about removing a wide area of mainly healthy tissue, and was therefore most interested to hear of Mr. P. G. Collins's method of treatment. Presumably the problem is not dissimilar to that of anal fistula, in the treatment of which I long ago abandoned the traumatizing excision that used to be taught, and have contented myself with laying open the tracks with diathermy, without removing any tissue at all. Healing is very much quicker, post-operative pain very much less, and final results just as good. A similar treatment may well be satisfactory with pilonidal sinus. I have not yet tried it, but must do so.—I am, etc.,

Upton Hospital, Slough. ROBIN BURKITT.

SIR,—I have followed the correspondence on the subject of pilonidal sinus, as I am surprised that it still presents a problem.

I was delighted to see that Mr. D. Lang Stevenson (*Journal*, September 12, p. 430) has once again reminded us of Oldham's method of primary suture. I can confirm Mr. Stevenson's statement that the technique is easy and can readily be learned by junior and inexperienced surgeons. In 1946 when I was a trainee surgeon in Hamburg under Mr. Stevenson he instructed me in the technique of primary suture in this condition. I performed this operation eight times during the following six years with 100% primary healing. I realize that this is a very small series, but even so I think it is significant.—I am, etc.,

London, W.1. R. P. GOULDEN.

Calcified Subphrenic Abscess

SIR,—I read with great interest the medical memorandum on calcified subphrenic abscess by Dr. A. C. Guan Khuan (*Journal*, August 29, p. 287). There were, however, several significant differences between this case and the case I described in 1957.[1]

The case I reported revealed no raising or deformity of the overlying right diaphragm, and screening showed the cyst to be lying within the soft-tissue shadow of the liver on antero-posterior, lateral, and oblique views. Tomography was unfortunately not possible. These points do, however, suggest that the cyst did in fact hold an intrahepatic position. The fact that a cyst some 3 in. (7.6 cm.) in diameter was situated under the diaphragm, which was neither displaced nor restricted in movement, and yet the liver remained impalpable, also points to an intrahepatic position.—I am, etc.,

Chester-le-Street, Co. Durham. ROBERT BRUCE.

REFERENCE

[1] Bruce, R., *Brit. med. J.*, 1957, **1**, 1343.

E.E.G. in Respiratory Failure

SIR,—I was interested to read the paper "Electroencephalographic Studies in Respiratory Failure" by Drs. L. A. G. Davidson and J. M. Jefferson (*Journal*, September 12, p. 396). As a rule, the mental changes and acute hypoxia which one sees in the emphysematous patient who has a severe chest infection commonly come and go together. I have been interested to see whether an emphysematous patient could suffer permanent cerebral damage from the acute hypoxia of a chest infection even though he had recovered from the latter. I have seen only one such case.

A man, aged 62, was slow, forgetful, and inclined to be truculent three months after a severe chest infection when he was extremely cyanosed, confused, and aggressive. The electroencephalogram, reported on by Dr. C. C. Evans of the Central Middlesex Hospital, showed non-specific changes which were compatible with irreversible brain-damage following anoxia. Three months later he reported on a repeat electroencephalogram which showed some degree of recovery and the

patient then was mentally normal apart from forgetfulness. This does suggest that he had not made a full recovery, because prior to his illness he was an excellent card-player.—I am, etc.,

Chase Farm Hospital, Enfield, Middlesex. THOMAS SIMPSON.

Telling the Cancer Patient

SIR,—I have had some experience with the care of patients suffering from the terminal stages of cancer over the past 12 years, working as a nurse, an almoner, and as a doctor. For the past year I have worked in two of the Terminal Care Hospitals, where I have known between three and four hundred patients. What I would like to say about this question applies to this particular group.

I am sure that we cannot make rules but that we must try and deal with each person individually. Our patients do not know the nature of the hospital when they come, and many do not ask a leading question at any time. As we almost always leave them to take the initiative, questions of their diagnosis and prognosis are not discussed. Our impression is that many of these people do realize at the end that they are dying and are able to accept the fact peacefully and quietly. Some like to talk of it, but others do not. Some, on the other hand, appear to keep their hope of recovery to the end.

There are many, however, who do ask us questions. A very few ask directly if they have cancer, for I think that by this time the actual diagnosis has less significance for them. Some wait until they know us well; a surprisingly large number ask on their first interview. I find that if my first answer is a rather guarded one, then the patient almost always goes on to give me a lead if he has a genuine desire for knowledge and shows me something of his real worries and fears and also of his ability to face up to a more direct and honest answer. Most of those who ask really want to know; very few indeed are unable to face the answer. The final truth may only come out in a series of talks. I have seen many whose real fear was not of cancer, nor of death, but of chronic illness, of pain, or of the uncertainty that often comes of deception. If, without taking away all hope of recovery, one is yet able to bring the idea of death forward as a strong possibility, some of the patient's real fears can be brought into the open and we can help him to deal with them. Many have expressed their gratitude for the truth at last, almost all say that they are not afraid, many accept spiritual help, some beginning to understand it apparently for the first time in their lives. Almost all grow in patience and courage until they die. Indeed, in these hospitals we see practically none in either group who die in fear, bitterness, or resentment. The nursing staff, nearly all with a real vocation for this work, can relieve suffering, both mental and physical, and the atmosphere is one of peace and attainment.

Relatives often ask that a patient should not be told, but they accept our assurance that while information will never be forced on patients it will be given if they really ask, and that, when they do realize the truth, we will be able to help. I have no space to quote cases, but I would like to assert most strongly that much good can come in some cases of the patient's knowing the truth, if at all times those telling it to him are trying to "speak the truth in love."—I am, etc.,

St. Joseph's Hospice, Hackney, London, E.8. CICELY SAUNDERS.

Cardiac Arrest

SIR,—We are reporting this case, not because any originality is claimed, but in the hope that it may encourage others faced with a similar catastrophe to attempt this method. Neither of us had any previous first-hand experience of cardiac massage.

The patient was a female, aged 38 years, who had been admitted to hospital six months previously with respiratory poliomyelitis. Her progress has been satisfactory and she had been out of the respirator for periods of up to 6–10 hours. Eventually she was out of the respirator completely for two days. On the morning of the third day she was a little dyspnoeic and was replaced in the respirator. The dyspnoea continued with evidence of paradoxical respiration and tracheal tug, and *x*-ray revealed collapse of the right upper lobe.

A small endotracheal tube was passed and tracheobronchial toilet performed with some improvement, and it was decided to perform bronchoscopy under general anaesthesia the next morning. Premedication was with atropine gr. 1/100 (0.65 mg.) given intravenously. Anaesthesia was induced with 100 mg. thiopentone and 50 mg. suxamethonium chloride. An airway was inserted and oxygen given by manual compression of the rebreathing bag for approximately two minutes. An attempt was then made to pass the adult Magill bronchoscope, but this proved to be too large and was withdrawn. A No. 7 cuffed endotracheal tube was passed for the purpose of re-oxygenating the patient. Unfortunately the rebreathing bag split and mouth-to-tube inflation was carried out for about 30 seconds while a new bag was procured. At this point her pulse became imperceptible and there was pallor and mottling of the skin. After inflation with oxygen for a further 30 seconds gasping spontaneous respirations commenced and a faint thready pulse was palpable. It was then impossible to keep her inflated against the spontaneous respiratory movements, and a further 25 mg. suxamethonium chloride was given to relax her. This was immediately followed by complete collapse with widely dilated pupils and cardiac arrest. Vigorous inflation with oxygen brought no improvement. A scalpel was obtained, and one of us (E. T.) made a 5-in. (12.7-cm.) incision through the left 4th intercostal space, forcibly separated the ribs by hand and a Fergusson mouth gag (this was later replaced by a rib spreader), and inserted a hand to compress the heart against the under surface of the sternum. Massage was continued intermittently for about 10 minutes, the heart commencing to beat on three occasions and then petering out again before restarting permanently and maintaining a good, strong, but rapid beat, and spontaneous respirations returned. The wound now began to bleed and unsterile Spencer Wells forceps were applied to the bleeding-points. In the meantime an intravenous transfusion had been started by the house physician, commencing with noradrenaline 2 ml. in 500 ml. N saline, and followed by 500 ml. blood. We had also appealed for help from the chest surgeon, Mr. S. C. F. Stephenson, who now arrived, and we gratefully handed over command. A further 30 minutes was allowed to elapse before the chest was closed with underwater drainage. During the closure of the chest the patient showed signs of returning consciousness with movements of head, neck, and arms, and she was given 50:50 mixture of nitrous oxide and oxygen.

In view of the complications of intravenous transfusion and underwater drainage it was decided to change from a tank respirator to intermittent positive-pressure respiration, so a tracheotomy was performed.

Apart from some temporary visual disturbances and amnesia for recent events, she was none the worse for the experience. Her wounds healed with no sepsis despite the completely unsterile technique, and the left lung expanded and also the previously collapsed right upper lobe, perhaps due to the rigorous manual

inflation. One factor which we feel may have had some bearing on the development of cardiac arrest was that the patient was extremely apprehensive and frightened, and seemed to have a premonition of impending doom. The patient is now off mechanical respiratory aid for 16 hours a day.

Our thanks are due to Mr. S. C. F. Stephenson and the team from Yardley Green Chest Hospital, to the theatre personnel for rising to the occasion, and to Dr. F. L. Ker for his assistance and permission to publish this case.

—We are, etc.,

EUGENE THOMAS.
KATHLEEN G. WRIGHT.

Little Bromwich Hospital, Birmingham, 9.

Jaundice after Prochlorperazine

SIR,—In the medical memorandum entitled "Jaundice During Prochlorperazine Therapy" by Drs. D. J. Deller, I. A. Brodziak, and A. D. Phillips (*Journal*, July 25, p. 93) it is stated that there has been no mention in the literature about jaundice following the ingestion of prochlorperazine. Coincidentally, in the *Journal of the American Medical Association* of August 1 appeared a communication on the so-called second case of jaundice as complication of the therapy by this drug[1]; in the references of this article there is one which seems to be the real first case in the literature[2] of cholangitis after administration of prochlorperazine.—I am, etc.,

Caracas, Venezuela. SERGIO ARIAS.

REFERENCES

[1] Weinstein, A., Alper, B. J., and Dade, J. R., *J. Amer. med. Ass.*, 1959, **170**, 1663.
[2] Mechanic, R. C., and Meyers, L., *New Engl. J. Med.*, 1958, **259**, 778.

Alpha-Chymotrypsin in Cataract Surgery

SIR,—Your very interesting annotation on zonulysis mentioned the original work of Barraquer, but omitted another original part of the technique which, although small in importance compared with the zonulysis, has been a great asset to the operation (*Journal*, August 1, p. 120).

I refer to Laurie's manœuvre—a simple manœuvre almost annoying in the way its success deprives one of the thrill of a difficult tumble. It is not too much to say that the three basic manœuvres of future difficult extractions may be Macaskill's right-angled section, Barraquer's zonulysis, and Laurie's iris retraction. It will be interesting also to see whether masters of the older intracapsular method like Macaskill and Barraquer will revert to tumbling.—I am, etc.,

Bath. T. S.-B. KELLY.

Queen's Institute of District Nursing Appeal

SIR,—Thank you for your reference (*Journal*, June 13, p. 1521) to the Centenary Appeal for £250,000 which has been launched this year by the Queen's Institute of District Nursing. The skilled and devoted work of this great voluntary nursing service is well known to doctors. In England and Wales alone in 1957 district nurses made over 25,000,000 personal visits, an average of more than one to every two persons.

In 1889 Queen Victoria granted the Institute a Royal Charter to promote and advance the recruitment and training of district nurses with a view to ensuring the provision of nursing of a high standard in the homes of the people. This task remains substantially the same to-day. Queen Victoria endowed the Institute with a large part of the Women's Offering at her Jubilee, and since then it has carried out its work largely with funds received from voluntary sources. Increasing costs, however, and the need to expand the work to meet the special demands and conditions of to-day have made it vitally necessary for the Institute to appeal for money.

The number of district nurses trained annually has risen to over 700. While fees are received from local health authorities, these cover only part of the Institute's heavy costs in connexion with training. More trained administrators and tutors are needed to meet these requirements. In 1960 the Institute is to open an administrative staff college in Liverpool, and the Nuffield Provincial Hospitals Trust has made a generous grant of £15,000 to assist in getting it started. Funds are urgently needed also to meet the increasing number of requests to pioneer and develop district nursing services overseas. This is becoming a most important development in the Institute's work, and district nursing associations have already been set up in Malta, Jamaica, and Tanganyika. The Institute is consulted by, and assists, a very large number of other countries both in and out of the Commonwealth. Through this work it is bringing the district nurse into homes which have known nothing like her before. The Q.I.D.N. has also heavy responsibilities towards sick and retired district nurses in financial need, including those who are too old to qualify for present-day superannuation schemes. Funds earmarked for this purpose fall short of requirements. New films are needed both for educational purposes and for showing to public audiences, wages and salaries have risen, and it has become necessary for the Institute to purchase the lease of its offices. In 1958 the Institute had a deficit of over £6,000, and sufficient capital must now be raised to ensure that income shall meet expenditure in future years.

The success of this appeal will mean that a great body of voluntary effort and financial support can be kept behind the district nursing service, and that the Queen's Institute can continue to carry out its task side by side with the National Health Service authorities. We therefore ask your readers to help us by sending a small donation either direct to the Q.I.D.N., 57, Lower Belgrave Street, S.W.1, or to the Hon. Treasurer, M. J. Babington Smith, Esq., C.B.E., Messrs. Glyn, Mills and Co., Kirkland House, Whitehall, S.W.1. We should also be grateful for any assistance that can be given to the appeal locally by individuals.—I am, etc.,

London, S.W.1. TERENCE AIREY,
Centenary Appeal Organizer,
Queen's Institute of District Nursing.

Qualification in Medicine

SIR,—I deplore the suggestion of Dr. G. O. Morse (*Journal*, August 15, p. 190) supported by Dr. J. R. Rees (September 5, p. 367) that we should, in order to impress the Americans and others, debase the coinage of British academic qualification by conferring a higher medical degree on all newly qualified medical practitioners.

In the general field of qualification nomenclature it is the Americans who are inconsistent in awarding the M.D. to their neophyte medical graduates, not ourselves. Apart from the resentment that would be caused to those who already hold an orthodox M.D., I wonder if your correspondents have considered the academic standards required for (say) the D.Sc. or Mus.D.—I am, etc.,

Shenfield. I. M. LARKIN.

SIR,—The letter of Dr. G. O. Morse (*Journal*, August 15, p. 190) deserves some criticism in favour of the

London examining bodies. Let us realize this is the age of equality and communal activities, but why must an originally high standard be lowered? What is wrong with the M.B., B.S.? Is the recipient ashamed of the degree? Why does he want an M.D.(Lond.) degree given for general medical qualifications?

The M.D.(Lond.) could formerly be taken by written examination as well as by thesis. At present, the thesis alone is sufficient for the degree. This gives strong evidence of the recipient's practical application to well-investigated research which has, of necessity, to be over a period of seven years. Perhaps there are some who have the M.D.(Lond.) who will endorse my remarks with more effect in preserving a very old and well-respected university degree in medicine.

Dr. J. R. Rees (*Journal*, September 5, p. 366) in his letter appears to want to lower the M.D.(Lond.) to the level of that of the general medical qualifications obtained by passing final examinations completing a doctor's training. Is this not a levelling of the socialist mind? Is the gorgeous colour of the academic dress too distinctive? Notice how the superabundance of the diplomas is intensely muddling to foreigners on the one hand; whereas, on the other hand, what could be simpler to understand than the degree of M.D.(Lond.) which so well expresses a doctor of medicine? The degrees M.B., B.S. and M.B., B.Ch. express knowledge of medicine and surgery of a well-qualified doctor.

In this modern world of abbreviations, let us not lose explicit specialist titles given by our revered Royal College of Physicians. Destroy the useless and ugly but leave the good unchanged. In Law and Philosophy the degree of doctor is the highest obtainable. Why should the medical world wish to alter its value?—I am, etc.,

London, W.1. MARJORIE M. DOBSON.

SIR,—With regard to the letter from Dr. J. R. Rees, F.R.C.P., of London, W.1 (*Journal*, September 5, p. 366), the international confusion caused by our varied degrees is certainly regrettable, but I would be against much standardization at home. For instance, in the unlikely event of letters on the same topic, in the same journal, from persons of the same name, it is reassuring to know that they may be readily distinguished by the small but important variations in the titles awarded by the Royal College of Physicians. In the present case, this is surely a better way to demonstrate seniority than by equally small (but perhaps equally significant) differences in postal districts.—I am, etc.,

London, S.W.1. J. R. REES.

Anaesthesia for Bronchoscopy

SIR,—May I comment on the several correspondents on my paper entitled "Hazards with Local Anaesthetics during Bronchography and Bronchoscopy" (*Journal*, March 14, p. 695)? I did not try to discredit any particular method and my honest intention was to point out the hazards of amethocaine and lignocaine, particularly the former. At the time of incidence, I was told that there was no reported calamity due to lignocaine. I confirmed this from one of the makers. Later, however, I found four cases of anaphylaxis[1] and one death[2] reported due to lignocaine.

Excellent reviews have been made regarding the dangers of amethocaine[3] on men and some experimental animals.[4] Hazards due to lignocaine have not been discussed widely. To avoid these incidents, several factors should be remembered: first, a history of allergic disorders should be sought in each case and too much reliance should not be put on skin sensitivity tests[5] (unless positive); secondly, a barbiturate should be given as a premedication[6]; thirdly, amethocaine should be replaced by lignocaine whenever possible (as suggested by Dr. J. A. Kellock, *Journal*, May 9, p. 1241); fourthly, safe limit of dosage must never be exceeded and this should never be administered through a catheter into the lower respiratory tract[4]; fifthly, a vial of thiopentone, oxygen apparatus, and respiratory stimulants should always be kept at hand, in cases of possible emergency; and, lastly, a mixture of adrenaline and local anaesthetic has not yet proved to be any superior to the latter alone.

With a barbiturate premedication, the incidence of reactions to amethocaine is about 1 in 600 cases.[6] Once the reaction develops, the best treatment is artificial respiration (as respiratory failure is a common cause of death,[4] especially with lignocaine[2]), oxygen, and maintenance of blood pressure. In convulsive cases, intravenous thiopentone is very effective. In cases of obvious respiratory failure, liquor adrenaline hydrochloride (B.P.) has no effect.[7]—I am, etc.,

London, N.4. SAMIR KUMAR GUPTA.

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Printing the "B.M.J."

SIR,—May I be allowed, necessarily belatedly, to express thanks for the efforts of yourself and your staff in successfully continuing to publish the *B.M.J.* in the interests of the profession and the public weal. You gave us articles of the greatest importance to both; for me the most interesting was Sir Arthur Thomson's Linacre lecture, historical, philosophical, practical, and wholly fascinating. He showed us (*Journal*, August 8, p. 130) the different eras, and taught us not to despise the slow degrees by which medicine did ascend; he reviewed our tenuous memories of far-off forgotten things; through his eyes we see again the great Achilles whom we knew: and now he poses before us the problems of the profession in relation to social and economic pressures; all this is equally as important as the polio vaccine or an anaesthetic machine.

To a Scot, it is curious that one who spells his name without a "p" should not refer to the Scottish school's application of physick as a therapy. Shades of Cullen, Christison, and Gregory. I can only quote his illustrious namesake and say, "Oh, Jimmie Tamson, Jimmie Tamson, Oh!" Would Sir Arthur agree that one dangerous tendency is creeping in? Too often we see various expensive and timetaking investigations of blood, urine, basic metabolic rate, and so on, being made before a careful history and clinical examination are made; in one clinic in the States I saw an instance where 0.1% excess of plasma uric acid led to a primary diagnosis of gout and the patient being given colchicine; he was suffering from metastatic septic arthritis. I am certain that there is still much to be learned from our forebears. Over 50 years ago a Musselburgh fishwife came back to Professor Wyllie's ward for review (she had suffered from gall-bladder trouble but was much better). Old John: "Hae ye got onything the matter wi' ye noo?" Patient: "Naw, Professor, but can ye no tell us what tae dae, A'm

getting that stout?" John, patting the dame on the shoulder, and still holding to the Doric, said, "Wumman, if ye dinna pit it in, ye winna pit it on." Do we know so much more about obesity now?

The Editor's trousers (*Journal*, August 8, p. 149) can doubtless be replaced, I hope on an expense account; as for the Business Manager's eyebrows—I had some association with one of the film companies, and might be able to arrange that he borrow a pair of falsies.—I am, etc.,

Drayton Valley, Alberta. W. GRANT WAUGH.

Mannomustine Therapy

SIR,—Mr. Anthony Green in his letter (*Journal*, September 12, p. 429) is surely not serious when he complains that "cytostatic remedies have never really cured a malignancy." No such claims have ever been made, and it is surely needless to point out that there are no cures, only treatments.

Chemotherapeutic agents are most useful, of course, in disseminated and widespread malignancies where radiotherapy cannot easily be employed, and, while the limitations of all methods of treatment are recognized, the remission of symptoms, diminution of pain, and prolongation of life—all accepted findings by the Hungarian workers and confirmed by Dr. John F. Wilkinson and his colleagues (*Journal*, August 22, p. 208)—are sufficient justification for using "degranol" (mannomustine) in suitable cases.—I am, etc.,

London, W.1. H. YARROW,
Managing Director,
Leda Chemicals Ltd.
(Pharmaceutical Division).

The Customary Fee

SIR,—I should be glad of your opinion—and of your readers'—as to what is now the accepted custom in the treatment of one doctor by another as regards paying fees for treatment.

Recently, when staying in the South of England, a doctor who retired 12 years ago and is now 89 was taken ill and seen by a local doctor, who, two days later, called in a consultant who had him removed to a private ward in the local general hospital and attended him there almost daily for three and a half weeks, giving him the most thorough physical examination, and having him *x*-rayed and put through other modern cardiological tests. He was then removed to a convalescent home, where he was for five and a half weeks. Apart from the heavy payment for the private hospital ward and the room at the convalescent home, the doctor charged a fee of 60 guineas, which was at once paid.

I would like to know if that is the usual custom nowadays for a doctor—whatever his status—to charge another doctor such a heavy fee, though in this case it was mostly recovered through a provident insurance agency.—I am, etc.,

Sheringham, Norfolk. W. R. SMITH.

Carcinoid Tumours Wanted

SIR,—I would be very grateful to obtain large amounts of carcinoid tumour tissue from patients with the full "flushing" syndrome. The tissue should be as fresh as possible and arrangements would be made to collect it.—I am, etc.,

Medical Unit,
St. Mary's Hospital,
London, W.2 W. S. PEART.

Obituary

D. H. GEFFEN, O.B.E., M.D., D.P.H.

Dr. D. H. Geffen, medical officer of health for the Metropolitan Borough of St. Pancras, died on September 17, aged 61.

Dennis Herbert Geffen was born in London on March 3, 1898, and was educated at University College School and University College Hospital, graduating M.B., B.S., with honours in pathology, in 1919. He proceeded M.D. in 1921, and obtained the D.P.H. in the same year. After holding the posts of house-physician and obstetric assistant at his teaching hospital and other resident appointments elsewhere, he entered the local government service, working first for the London County Council and later in Poplar and Finsbury. In 1927 he was appointed medical officer of health for the Borough of Enfield, and in 1944 he became medical officer of health for the Metropolitan Borough of St. Pancras. To broaden his knowledge he read for the bar, and was a member of Gray's Inn.

Dr. Geffen was quite outstanding for the time and energy which he put into his work in public health and for his wide interest in all branches of this field of medicine. His great interest was in the maternity and child-welfare services, and his books on this subject are widely used, particularly abroad in the Mediterranean area. He was the honorary secretary and later chairman of the executive committee of the National Baby Welfare Council. Although it was a keen disappointment to him when the maternity and child-welfare services were transferred to the London County Council in 1948, he maintained a great interest in the clinics and other services in his borough. He was a lecturer on public-health subjects at University College Hospital and the Hospital for Sick Children, Great Ormond Street, and he also lectured to the D.P.H. class at the London School of Hygiene and Tropical Medicine. His clear and forceful lectures will be well remembered by many graduates. He also lectured on child welfare in the United States in 1949. In recent years he was a member of the Board of Governors of the Royal Free Hospital, and in 1954 he was appointed O.B.E.

He was a shrewd and capable epidemiologist, and among his investigations and reports perhaps the most notable are those dealing with the relationship between the site of injections and subsequent paralysis in poliomyelitis. His investigation, with the help of Dr. Susan Tracy, of the outbreak of acute encephalomyelitis in the Royal Free Hospital Nurses' Preliminary Training School was published in this *Journal*, as was also his inquiry into the incidence of poliomyelitis in children under 6 months. As a generous and helpful colleague, his wide knowledge of medicine and of public health was freely available to all. He was elected president of the Metropolitan Branch of the Society of Medical Officers of Health for the year 1957–8, and he was chairman of the Metropolitan Borough Medical Officers' Committee at the time of his death. As a wide and knowledgeable adviser, a pleasant companion, and a delightful host he will be sorely missed by his many friends and colleagues, who will wish to extend their sympathy to his widow and two sons.—R. D. D.

A memorial service for Dr. Geffen will be held on Tuesday, September 29, at 6 p.m., at New West End Synagogue, St. Petersburg Place, London, W.2.

C. V. GRIFFITHS, C.B., C.B.E., D.S.O. M.R.C.S., L.R.C.P.

Surgeon Rear-Admiral C. V. Griffiths died at Chichester on September 12 at the age of 76.

Cyril Verity Griffiths was born on March 26, 1883, at Bermuda, the son of Richard S. P. Griffiths, R.N., Inspector-General of Hospitals and Fleets. He studied medicine at King's College Hospital, and after qualifying in 1906 he held the appointment of house-surgeon there until he entered the Navy as surgeon in May, 1907. Before the first world war he served in H.M. Ships *Prince George* and *Prince of Wales* and at the Royal Hospital, Cape of Good Hope. He was promoted surgeon lieutenant - commander in 1914.

[*Walter Stoneman*

During the first world war he served in H.M. Ships *Shannon, Lord Clive,* and *Weymouth* and was awarded the D.S.O. in December, 1918, for services in action during the war. He was promoted to the rank of surgeon commander in 1918. Between the two world wars he served in various hospitals and ships and was promoted surgeon captain in 1931. He was principal medical officer of *H.S. Maine* from 1931 to 1933, and for some years he was medical officer-in-charge of the Royal Naval Hospital, Portland.

Promoted surgeon rear-admiral in December, 1937, he served during the whole of the second world war at the Admiralty as Deputy Medical Director-General. He was King's Honorary Physician from 1940 to 1946, and in 1941 he was appointed C.B. Placed on the retired list on reaching the age of 60 in 1943, he continued to serve until his release in 1946. He was appointed C.B.E. in 1946.

Admiral Griffiths was a good mixer and an exceedingly kindly and popular officer. He travelled a great deal during the last war on inspections of ships and establishments and he was always very warmly welcomed. His main recreation was walking, and a 12-mile tramp meant nothing to him.

He was twice married. His first wife, formerly Muriel Joy Beaumont, by whom he had one son, died in 1927. In 1946 he married Frances Rosemary Brocklehurst, who survives him. He remained active and enjoyed life to the end. His very many friends will miss him greatly, and our deep sympathy is extended to his widow.

NORBERT ESSIGMAN, M.D.

Dr. Norbert Essigman, who had been in practice as an ophthalmic surgeon in London since the end of the second world war, died on August 4, aged 64.

Norbert Essigman was born in Warsaw and graduated in medicine at the university there. Deciding to specialize in ophthalmology, he worked for about fifteen years in an eye hospital. He was an active member of the Polish Ophthalmological Society, and took part not only in the medical work but in social work as well. During the second world war he served in the Polish forces under British command in the Middle East and in Italy, where he was in charge of the ophthalmic department of one of the Polish military hospitals. In 1946 he came to the United Kingdom and settled in London as an ophthalmic surgeon. His wife died three years ago, and he never recovered from this grievous loss. A good surgeon and a man of kind heart, he will be missed by his many patients, both British and Polish. He is survived by a son, also a doctor, and a younger daughter, to whom the deep sympathy of his friends and patients is extended in their bereavement.—M. M.

HELEN FLANDERS DUNBAR, M.D., Ph.D.

Dr. Flanders Dunbar, who practised as a psychiatrist in New York and was well known as the author of books on psychosomatic medicine, was drowned last month in the swimming-pool of her home at South Kent, Connecticut.

Helen Flanders Dunbar was born in Chicago on May 14, 1902. Educated at Bryn Mawr College, she graduated Ph.D. at Columbia University in 1924 and M.D. in 1930. As a postgraduate she studied psychiatry in Vienna and Zurich, and later she became an instructor in psychiatry at Columbia University and a visiting psychiatrist at the Presbyterian Hospital, New York. For many years she had carried out research into psychosomatic medicine, a subject on which she was regarded as a leading authority. Her first book, *Symbolism in Medieval Thought,* was published in 1929. Her best-known work, *Emotions and Bodily Changes,* first appeared in 1935 and is now in its fourth edition. For nearly ten years she was editor-in-chief of *Psychosomatic Medicine,* and she was the author of many papers on psychiatric subjects.

N. A. A. HUGHES, M.R.C.S., L.R.C.P.

The obituary of Dr. N. A. A. Hughes was published in the *Journal* of August 22 (p. 250).

H. F. writes: Norman Hughes was a typical first-rate country G.P. with an extensive practice as well as a wide circle of friends. Shortly after he went into practice he decided to become a total abstainer, and he remained one for the rest of his life. His interests were many. A vicar's son himself, he was vicar's warden at the Parish Church of Calverley for nearly 30 years, and he took an active part in village affairs. For many years he was president of the West Riding County Amateur Football League, of which he was joint founder, and he was a former president of the Calverley Association Football Club and of St. Wilfred's Cricket Club and of the Calverley branch of the British Legion. On his retirement in 1946 he moved to Menston-in-Wharfedale, where he was able to devote himself to his two dearest pursuits, chrysanthemums and Freemasonry. He died after a full and happy life.

Medico-Legal

THE LAW SOCIETY ON ARTIFICIAL INSEMINATION

[FROM OUR LEGAL CORRESPONDENT]

The council of the Law Society (assisted by two lady solicitors not members of the council) has submitted a memorandum to the Departmental Committee on Artificial Insemination set up under the chairmanship of Lord Feversham.

The council recognizes that the main arguments for and against artificial insemination are medical, psychological, social, and religious rather than legal. It believes that no difficulties of principle on these grounds arise in the case of homologous insemination (artificial insemination by the husband: A.I.H.). Such difficulties are, however, likely to arise in the case of heterologous insemination (artificial insemination by a donor: A.I.D.; or artificial by a donor and the husband: A.I.D. and H.). However, the only way of forbidding such artificial insemination would be by making it a criminal offence. This would be undesirable, as the law would be unenforceable, and would tend to encourage resort to unqualified practitioners. The council has therefore assumed for the purposes of its memorandum that artificial insemination ought to be tolerated within limits and subject to controls. It considers what those limits and controls ought to be, and suggests answers to the legal problems arising out of artificial insemination.

Recommended Legislation

The effect of artificial insemination in matrimonial law as it stands at present is doubtful. The council recommends legislation to the following effect. The voluntary reception of insemination from a donor alone (A.I.D.), without the consent of the husband, should be a matrimonial offence and a ground for divorce, and such an offence should be regarded as condoned where the husband subsequently receives the child into the family with the knowledge that it was conceived through A.I.D. On the other hand, the failure on the part of a donor to obtain his wife's consent to his acting as a donor should be a new and separate ground of divorce at the instance of the donor's wife. The council does not recommend a statutory procedure for obtaining the wife's consent, but considers that it should be intimated to the medical profession that, before taking a donation from a married donor, the medical practitioner should satisfy himself that the wife of the donor has genuinely consented to the donor giving his services. The council feels that this should be a matter of professional ethics. The council also recommends that where a child is born as a result of artificial insemination to which the husband has consented, nullity proceedings by either spouse on the grounds of inability or wilful refusal to consummate should not be entertained, but that nullity proceedings should be permissible where the artificial insemination is unsuccessful.

As regards the status of the child and its relationship with its parents, the council recommends that, in the case of a child conceived during the life of the husband and with his consent, parental rights and duties, the child's rights of succession, and the form of registration of birth should be exactly the same as for a legitimate child conceived in normal circumstances. However, any A.I.H. child conceived after the death of the husband as a result of his semen being stored in a deep-freeze bank should be illegitimate, otherwise grave complications of succession and in the winding up of estates would result. Moreover, where the presumption of legitimacy is rebutted (i.e., where it is proved that the husband has not consented and that he could not be the father) the child should remain illegitimate, and acceptance of the child by the husband ought to leave its status unchanged unless followed by a formal adoption order.

Medical Control

The council recommends certain controls on the administration of artificial insemination. It should not be practised by any person who is not a registered medical practitioner: this provision should be supported by criminal sanctions. The medical profession should be invited to consider whether the practice of artificial insemination ought to be restricted to a panel of specialists normally engaged in this work; and, if so, a direction should be made that it would be unethical conduct for any medical practitioner not on the panel to engage in any kind of artificial insemination treatment. The selection of donors should remain exclusively in the hands of the medical profession, and the name of the donor should be known only to the doctor taking the donation.

Obtaining Consent

Some provision should be made for a formal procedure for obtaining the consent of husband and wife. This procedure should combine secrecy with a formality that is sufficient to impress the parties with the seriousness of their act without acting as a deterrent.

The procedure recommended is that the husband and wife should appear before a county court registrar or a chancery master of the High Court in chambers, where they should produce a medical certificate certifying the case to be suitable for artificial insemination. The court official would explain the legal consequences of their decision and interview them either singly or together. Both husband and wife would then sign an official form of consent. A Consent Order would then be drawn up and filed at the court (but would not be open to inspection without the leave of a High Court judge), and a copy would be given to the parties for presentation to the doctor, who, after reading it, would be required to destroy it.

The council considers that the same procedure should apply to unmarried women who wish to receive artificial insemination. It does not think it would be advisable to forbid unmarried women to receive artificial insemination, owing to the difficulty of enforcing any such provision by criminal sanction. It recommends, however, that no Consent Order should be made in favour of an unmarried woman less than 25 years old.

If the council's consent procedure is adopted, the council recommends that it should be a criminal offence for anyone to receive, administer, or assist in administering artificial insemination otherwise than in accordance with that procedure.

Vital Statistics

Week Ending September 12

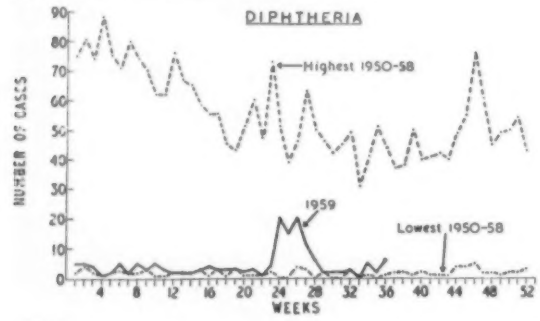
Infectious Diseases

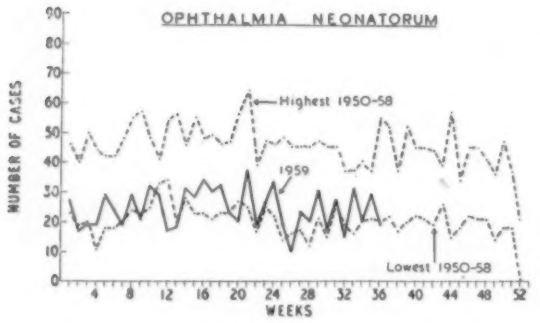
Areas where numbers of notifications were high in the latest two weeks for which figures are available

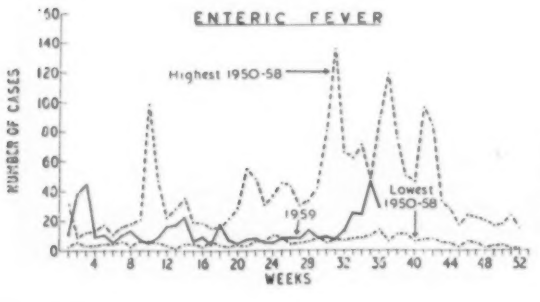
	Week Ending Sept. 5	Week Ending Sept. 12
Diphtheria		
London A.C.	0	6
Finsbury M.B.	0	6
Measles		
Lancashire	152	191
Accrington M.B.	0	18
Horwich U.D.	9	21
Prescot U.D.	0	11
Tyldesley U.D.	14	37
Nottinghamshire	15	30
Basford R.D.	0	6
Bingham R.D.	0	6
Acute Poliomyelitis		
London A.C.	6	6
Hampshire	2	5
Lancashire	5	5
Yorkshire North Riding ...	1	3
Dysentery		
London A.C.	28	47
Poplar M.B.	0	14
Yorkshire East Riding ...	25	28
Kingston upon Hull C.B. ...	17	16
Haltemprice U.D.	8	12
Food-poisoning		
Devon	5	20
Lynton U.D.	0	19
Warwickshire	7	16
Coventry C.B.	0	11
Cheshire	6	13
Bebington M.B.	0	7
Typhoid Fever		
Essex	0	2
Hornchurch U.D.	0	1
Ilford M.B.	0	1
Lancashire	1	2
Liverpool C.B.	0	1
Thornton Cleveleys U.D. ...	0	1
London A.C.	0	3
Hampstead	0	3
Paratyphoid Fever		
Caernarvonshire	12	6
Caernarvon M.B.	12	5
Ogwen R.D.	0	1
Acute Infectious Encephalitis		
Durham	0	4
Gateshead C.B.	0	4

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 5** (No. 35) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

* The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	0	1	0	3	0	0	1	0	
Dysentery	387	28	253	7	1	376	41	150	17	3
Encephalitis, acute	4	0		0		4	1		0	
Enteric fever:										
Typhoid	6	0	0	2	2	6	1	1	0	
Paratyphoid	42	4	1 (B)	0		4	1	0	0	1 (B)
Food-poisoning	415	34	36	3		397	31	37	1	
Infective enteritis or diarrhoea under 2 years				14	58				14	28
Measles *	1,236	43	14	24	32	2,810	199	12	17	39
Meningococcal infection	13	2	24	0		10	0	9	0	
Ophthalmia neonatorum	29	3	7	0	1	21	0	3	0	
Pneumonia †	101	9	90	3	1	135	7	102	1	1
Poliomyelitis, acute:										
Paralytic	26	3	1	0	2	46	2	26	0	7
Non-paralytic	18	3	2			32	0			
Puerperal fever §	178	18	13	0		214	27	8	0	
Scarlet fever	248	248	58	9	13	286	24	44	11	10
Tuberculosis:										
Respiratory	377	39	60	14		447	48	53	30	
Non-respiratory	52	7	5	7		65	6	10	8	
Whooping-cough	873	42	191	7	48	810	53	78	63	17

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	1	0	2	5	0	1	0	0
Influenza	7	1	1	0	0	2	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	1		
Pneumonia	286	22	13	4	1	276	18	8	9	6
Poliomyelitis, acute	0	0		0	0	5	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	70	6	5	2	3	59	2	9	2	5
Non-respiratory		0	0	0	0		1	0	0	0
Whooping-cough	0	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	248	20	22	5	6	253	25	22	5	15
Deaths (excluding stillbirths)	7,436	577	481	110	114	7,889	632	460	76	142
LIVE BIRTHS	13,984	1193	926	234	388	13,570	1133	956	199	408
STILLBIRTHS	278	20	23			286	15	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

J. H. Burn Fellowship.—Professor J. H. BURN, F.R.S., retires from the Oxford chair of pharmacology this month after 21 years. Through his efforts during this period his department has become one of the most important centres of pharmacological research, and, in order to ensure that his name continues to be linked with the department, a fund has been established to endow a J. H. Burn Fellowship for research in pharmacology there. Professor G. A. H. BUTTLE, professor of pharmacology, School of Pharmacy, University of London; Dr. W. FELDBERG, F.R.S., head of the division of physiology and pharmacology, National Institute for Medical Research; and Professor Sir GEORGE PICKERING, regius professor of medicine, University of Oxford, have agreed to act as trustees of the fund and to devise regulations governing the award of the proposed fellowship.

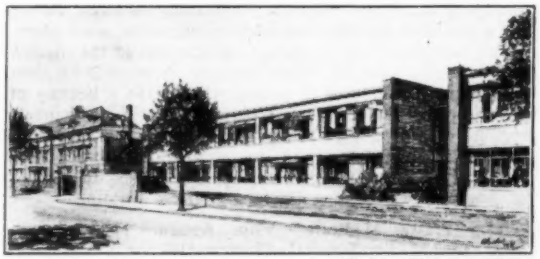
International Federation of Surgical Colleges.—A meeting of the Federation was held in Munich on September 15 and 16 under the chairmanship of Sir HARRY PLATT, at which working parties were set up to examine the following problems with which the Federation proposes to concern itself: surgical missions; training of surgeons; surgical research; and the interchange of young surgeons. The following new members were elected: College of Surgeons of Poland, Association of Surgeons of India, Association Française de Chirurgie, Societé Hellénique de Chirurgie, Austrian Surgical Society, and the Swiss Surgical Association. The Polish College of Surgeons' representative was elected to fill a vacancy on the executive committee. During an open meeting papers were read on "International Co-operation by Means of Sending Surgical Missions to Countries in Need of Them," and a report of this meeting will be published in due course. The Federation will next meet in London in October, 1960.

"Psychopharmacologia."—This new journal is intended to provide a medium for the speedy publication of scientific contributions concerned with the analysis and synthesis of the effects of drugs on behaviour, in the broadest sense of the word. These contributions may be clinical, or they may deal with specialized investigations in the fields of experimental psychology, neurophysiology, neurochemistry, general pharmacology, and cognate disciplines. The editors are Dr. A. WIKLER (National Institute of Mental Health, Addiction Research Center, U.S. Public Health Service Hospital, P.O. Box 2000, Lexington, Kentucky) and Dr. E. ROTHLIN, 6, Sonnenweg, Basle, Switzerland, to whom contributions should be sent. Dr. W. MAYER-GROSS (Birmingham) is a member of the international editorial board. The journal will be published at indefinite intervals to avoid delay in publication, and each issue will be priced singly. Details from the publishers, Springer Verlag, Berlin.

European League for Mental Hygiene.—The League's annual conference, on the theme of "Early Marriage and the Effects on Children of Young Parents from the Mental Health Point of View," was held in Barcelona on August 29 under the presidency of Professor HANS HOFF (Vienna).

Dr. DINO ORIGLIA (Italy), who gave the opening paper, said that early marriage was especially common in England, Scandinavia, and France, but relatively rare in Italy and Spain. It was favoured by lack of parental training in matters of health and in the responsibilities of living in the adult world, by competition among young people to marry and start a family, by failure of understanding between parents and children, and by lack of a comfortable and harmonious home background. Young parents, he said, were selfish, found their children a tie, and tended to punish harshly or to neglect them. Children of young marriages often married young themselves and passed on the bad pattern to succeeding generations. Public opinion at present, however, was in favour of early marriage. Professor J. DE MARAGES (Spain), who was an opponent of early marriage, opened the discussion. Defending, Dr. A. REPOND (Switzerland), Professor H. C. RUMCKE (Holland), and Dr. DORIS ODLUM (U.K.) felt that early marriage could be a stabilizing and integrating influence and provide an incentive to work and to become responsible. The importance of pre-marital education was also stressed. Dr. Odlum said that it was important above all to educate those such as medical students, who would ultimately be responsible for advising others. Professor C. DE SANCTIS (Italy) was installed as president for the next year, Professor P. SIVADON (France) elected as vice-president, and Dr. G. VAN LOOY (Holland) was appointed honorary secretary. The next meeting will be held in Edinburgh in August, 1960.

Llanelly Hospital.—The hospital's new 64-bed ward block, the Elizabeth Williams Memorial Wards, was opened on September 10 by Mr. F. J. TORRANCE BAKER, of the Fidelity Trust Company, Pittsburgh. The £103,000 wards



[Sir Percy Thomas and Son

were financed by capital raised under the terms of the late Mr. JOHN C. WILLIAMS's will. Mr. Williams, an American steel magnate, who died in 1936, was a native of Loughor, and worked in the Llanelly area as a steelworker before emigrating to the United States at the age of 21. The wards were named in memory of his mother.

Anglo-German Medical Society.—The Anglo-German Medical Society (Deutsch-Englische Ärzte Vereinigung) was founded on September 9 at a London meeting attended by about 70 German and British doctors (see correspondence, *Journal*, August 29, p. 307). It was agreed that the society's principal activity should be the collection of funds for furthering exchanges and visits between British and German doctors working in every branch of medical science and practice, and that it should also aim at providing a medical information service by means of a quarterly newsletter. The meeting then elected the following officials: *British Section:* President, Professor J. S. MITCHELL, F.R.S. (regius professor of physic, University of Cambridge); Vice-President, Professor W. A. MACKEY (Glasgow); Secretaries, Dr. E. KAWERAU (London) and Dr. W. WALKER (Dundee). *German Section:* President, Professor H. BENNHOLD (director, University Medical Clinic, Tübingen); Secretary, Dr. F. K. BELLER (Tübingen). The Foundation Meeting closed with thanks to Dr. EUGEN GÜRSTER (cultural attaché, German Embassy, London), who has for many years promoted interest in such a society for British and German doctors. Inquiries should be sent to Dr. E. KAWERAU, Department of Chemical Pathology, St. Mary's Hospital, London, W.2.

Western Regional Hospital Board Prizes.—In 1958 the Board agreed to provide annually, from its endowment resources, five essay prizes of £50 each which would be open to competition by registrars in the regional hospitals. The list of prize-winners for this year is as follows:

Dr. SHEDDEN ALEXANDER (Glasgow Royal Infirmary and Killearn Hospital): "Some Observations on Spinal Cord Injuries in Glasgow"; Dr. T. S. R. TRAIN (Cresswell Maternity Hospital, Dumfries): "*X*-ray Pelvimetry"; Dr. J. S. S. STEWART (Glasgow Royal Infirmary): "The Clinical Appearances and Aetiology of Klinefelter's Syndrome"; Dr. A. I. M. GLEN (Woodilee Hospital, Lenzie): "Photosensitivity in Long Stay Mental Hospital Patients"; and Dr. E. M. COLEMAN (Glasgow Royal Hospital for

Sick Children): "The Electrocardiogram in Idiopathic Hypercalcaemia and Other Disturbances of Cation Equilibrium in Childhood."

R.S.M.'s Richard Kovacs Prize.—The Council of the Royal Society of Medicine has recently accepted from Mrs. INA KOVACS, of New York, a sum of money which will make it possible for a Richard Kovacs Prize to be awarded triennially in memory of her husband. The prize, of £50, will be awarded first in 1961 by the Council of the Society, on the recommendation of the Council of the Section of Physical Medicine, for distinguished work in physical medicine during the previous three years. The award of the prize may, at the discretion of the Council of the Section, provide an occasion for the reading of a paper by the recipient at a meeting of the Section. Details of the form which applications for the prize should take will be announced later.

Photography in Medicine and Biology.—The Medical Group of the Royal Photographic Society of Great Britain has established an extensive bibliography of original papers on photographic techniques and applications in the medical and biological sciences. The honorary librarian is prepared to quote the references of papers which have a bearing on any problem concerned with photography in medicine or biology, free of charge, to all bona-fide inquirers. Detailed requests for references to the literature should be addressed to Mr. J. A. FAIRFAX-FOZZARD, M.A., F.R.P.S., the School of Anatomy, Cambridge University, Great Britain.

"La Presse Médicale" Film Award.—The "Annual Prize for Medico-Surgical Cinema (16 mm.)," given by *La Presse Médicale*, and various other prizes, will be awarded during the last session of "Actualités Médico-Chirurgicales" at the Nouvelle Faculté de Médecine de Paris on April 5, 1960. Films should be sent to the Secrétariat, *La Presse Médicale*, 120, Boulevard Saint-Germain, Paris, 6, from whom details may be obtained, before February 29, 1960. A new departure is that commercial films will be eligible for the award.

Dr. L. G. Norman, chief medical officer of London Transport, is visiting Australia and New Zealand from October 19 to December 14 at the invitation of the Post-graduate Committee in Medicine of the University of Sydney to discuss the medical aspects of road traffic accident prevention.

COMING EVENTS

Association of Clinical Pathologists.—63rd general meeting, Royal College of Surgeons, London, October 1, 2, 3. Details from Professor J. N. CUMINGS, the National Hospital, Queen Square, London, W.C.1.

Heberden Society.—Meeting and round, 2 p.m., October 2, Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London, W.12.

Middlesex Hospital Medical School.—The Annual Dinner for past and present students will be held at the Savoy Hotel on October 2, 7 p.m. The week-end refresher course for past Middlesex men will be from 2.15 p.m., October 2 to 4.

Midland Medical Society.—The Annual Dinner will take place on October 14 at the Birmingham Medical Institute, 36, Harborne Road, Edgbaston. Details from the Society at the Institute.

Manchester University.—Professor A. C. B. LOVELL, F.R.S., will give the Lloyd Roberts Lecture, "The Structure of the Universe," at 5.15 p.m., October 23, at the University.

British Hospitals Contributory Schemes Association (1948).—Annual conference, City Hall, Sheffield, October 29 to 30. Tickets from the Secretary, Mr. H. W. CLARKE, Sheffield and District Convalescent and Hospital Services Council, 38, Church Street, Sheffield, 1.

NEW ISSUES

British Heart Journal.—Issued quarterly (£3 annually). The new issue (Vol. 21, No. 3) includes:

THE CLINICAL USES OF OXIMETRY. Malcolm B. McIlroy.
A CLINICAL TRIAL OF PENTA-ERYTHRITOL TETRANITRATE, A KHELLIN DERIVATIVE (RECORDIL), AND IPRONIAZID IN ANGINA OF EFFORT. H. A. Dewar, A. R. Horler, and D. J. Newell.
IPRONIAZID IN THE TREATMENT OF ANGINA OF EFFORT. P. J. D. Snow and D. E. Anderson.
ANNULAR CONSTRICTIVE PERICARDITIS. Patrick Mounsey.
EFFECT OF DIGOXIN ON THE CIRCULATION IN NORMAL MAN. Arthur Selzer, H. N. Hultgren, C. L. Ebnother, H. W. Bradley, and A. O. Stone.
THE SIGNIFICANCE OF CHANGES IN THE ELECTROCARDIOGRAM IN HYPOTHERMIA. D. Emslie-Smith, G. E. Sladden, and G. R. Stirling.
MEASUREMENT OF THE ERROR IN WILSON'S CENTRAL TERMINAL. G. E. Dower, J. A. Osborne, and A. D. Moore.
HYPERTENSION AND UNILATERAL RENAL DISEASE TREATED BY NEPHRECTOMY. D. M. Douglas, K. G. Lowe, and R. G. Mitchell.
CARCINOID HEART DISEASE. John Cosh, J. E. Cates, and D. W. Pugh.
PERSISTENCE OF RIGHT VENTRICULAR HYPERTROPHY FOLLOWING MITRAL VALVOTOMY. R. V. R. Rodriguez Torres, J. Mackinnon, E. G. Wade, and C. F. H. Vickers.
ASSESSMENT OF MITRAL VALVE DISEASE BY LEFT HEART CATHETERIZATION. Ernest W. Hancock.
MEASUREMENT OF CARDIAC OUTPUT USING A RADIOISOTOPE AND A SCINTILLATION COUNTER. W. A. Seldon, J. B. Hickie, and E. P. George.
HIGH CHEST LEADS AND MINOR MYOCARDIAL INFARCTIONS. Hugo Roesler.
VALVOTOMY AS A CURATIVE OPERATION FOR SIMPLE PULMONARY STENOSIS. Maurice Campbell.
HYPERTROPHIC INFUNDIBULAR STENOSIS COMPLICATING SIMPLE PULMONARY VALVE STENOSIS. A. M. Johnson.
RAYMOND DE VIEUSSENS ON MITRAL STENOSIS. C. E. Kellett.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, September 29

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION—At Manson Theatre, London School of Hygiene and Tropical Medicine, 6.15 p.m., Dr. R. A. M. Case: Mortality Studies. Work in Progress.

Wednesday, September 30

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Multiple Handicaps. Miss J. E. M. Stephen, M.A., Dip.Ed.: Survey of a Group of Children with Mental and Physical Handicaps; Mr. M. Reed, B.Sc.: Deafness and Differential Diagnosis.

Thursday, October 1

SOCIETY OF CHEMICAL INDUSTRY.—At Lecture Theatre, Adam House, Edinburgh, 5.30 p.m., 6th Lister Memorial Lecture by Dr. Nathan B. Eddy (Maryland, U.S.A.): Chemical Structure and Action of Morphine-like Analgesics and Related Substances.

Friday, October 2

COLLEGE OF GENERAL PRACTITIONERS: SOUTH LONDON FACULTY.—At Meyerstein Lecture Theatre, Westminster Hospital Medical School, 8.15 for 8.30 p.m., Professor R. S. Illingworth: Prognosis.
HEBERDEN SOCIETY.—At Lower Lecture Theatre, Postgraduate Medical School, 2 p.m., scientific meeting.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. T. Holmes Sellors: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. Anthony Radcliffe: Tonsillectomy and Adenoidectomy.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. H. W. Balme: "A Visit to the U.S.A."

Saturday, October 3

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Grove Park Hospital, Lewisham, S.E., 10.30 for 11 a.m., Lecture Demonstration by Dr. L. M. Franklin and Dr. L. A. Nichols: Hypno-therapy in the Management of Chest Disease; Dr. Martin Nagley: Latest Developments in Tuberculosis Research. 2.30 p.m., annual general meeting.

Sunday, October 4

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Dr. W. Robinson: Bronchitis.
UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Clinical demonstration by Dr. T. D. Whittet: Survey of New Drugs and Preparations.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Bruce.—On August 26, 1959, in a road accident in France, Lewis Stuart Bruce, M.B., Ch.B., of Eristort, Blairgowrie, Perthshire, aged 45.
Dowds.—On August 21, 1959, at King Edward VII Hospital, Midhurst, Sussex, John Alexander Dowds, M.B., B.Ch., aged 57.
Gallegos.—On August 22, 1959, in hospital, Octavio Pacifico Gallegos, M.R.C.S., L.R.C.P., of 368, Uxbridge Road, West Acton, London, W.
Hall.—On August 25, 1959, at Fleet, Hants, Ernest Hamilton Hall, O.B.E., M.B., B.Ch., D.P.H., Major-General, R.A.M.C., retired.
Higson.—On August 17, 1959, William Davies Higson, M.B., Ch.B., D.P.H., aged 80.
Jones.—On August 20, 1959, at Hafodynys, Rhewl, Ruthin, Denb, Thomas Owen Jones, L.R.C.P.&S., aged 88.
Rawson.—On August 15, 1959, at 9, Park Drive, Heaton, Bradford, Yorks. William Foster Rawson, F.R.C.S.Ed., F.R.C.O.G., aged 87.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Foot-drop After Labour

Q.—*What is the treatment for pains in the leg and foot-drop after forceps delivery in cases of obstructed labour?*

A.—While pains in the leg and foot-drop may be produced by pressure on the nerves within the pelvis the prolapse of a disk during labour is not unknown, and it is important by examining the back, by straight-leg raising, and by ascertaining the anatomical distribution of the peripheral nerve changes to exclude this cause of the symptoms. If, as is probable, there has been pressure on the peripheral nerves within the pelvis, the treatment will follow the ordinary lines of peripheral nerve injury.

The injury is likely to be either an interruption of the myelin sheath, which will recover in a few days, or more probably of the axon itself. After interruption of the axon a regeneration of this structure is initiated from the proximal end, and it will grow down the leg at the rate of approximately 1 in. (2.5 cm.) a month. There is no need to fear that the nerve is anatomically interrupted in a gross sense, and recovery may be expected. Contracture is unlikely, and the only treatment necessary is a drop-foot spring to make walking easier until recovery occurs. Other forms of splintage and electrical stimulation of the paralysed muscle are not essential. The pains are likely to disappear, but meanwhile may be treated with analgesics.

Sulphuric Acid Burns

Q.—*What is the immediate and subsequent treatment of small burns of the skin caused by concentrated sulphuric acid?*

A.—Immediate treatment is to minimize further damage by washing off any remaining acid as quickly as possible—a few seconds may make the difference between a burn or no burn. In practice it is usually best to wash with copious amounts of tap-water. Delay may be caused if an appropriate "antidote" such as lime-water has to be found. However, if chemical burns are a frequent hazard, a phosphate buffer solution of KH_2PO_4, 70 g., and $Na_2HPO_4.12H_2O$, 180 g., in 850 ml. water is useful for both acid and alkali burns.[1]

The later treatment of burns due to acid is similar to that of thermal burns. A local antibiotic cream and a closed dressing incorporating a cotton-wool or other bacteria-proof layer is probably the treatment of choice. Sterile dry dressings or tulle gras are alternatives for application to the damaged surface. Areas of full-thickness loss of 1 in. (2.5 cm.) or more in diameter should have split-skin grafts applied. This can be conveniently done 2–3 weeks after injury, though good results can be obtained earlier by excision and grafting immediately after injury, provided that the diagnosis of full-thickness loss can be made with confidence.

REFERENCE

[1] Poser, E., and Haas, E., *J. Amer. med. Ass.*, 1943, **123**, 630.

Climate and Multiple Sclerosis

Q.—*Has climate any influence on the course of disseminated sclerosis? Might a semi-ambulant patient expect any improvement should he move to a Mediterranean climate?*

A.—There appears to be a definite geographical incidence of disseminated sclerosis, but whether this depends on climatic, dietetic, or other factors is unknown. It is a relatively common disease in Europe, but cases are rare in South Africa[1] and in India. In the North American continent cases appear to be more frequent in Canada and in the northern states of the U.S.A. than in the southern states, and it has been said that "all of the states or provinces with high rates either touch or are north of the fortieth parallel."[2] As regards an established case, it is unlikely that a move to a Mediterranean climate would have any specific effect on the disease process.

REFERENCES

[1] Dean, G., *Brit. med. J.*, 1949, **1**, 842.
[2] Limburg, C. C., *Ass. Res. nerv. Dis. Proc.*, 1950, **28**, 15.

Toxicity of Epoxy Resins

Q.—*Is food which has been exposed to minute quantities of amine-catalysed resins rendered unfit for consumption?*

A.—On the evidence available at the present time, food which has been in contact with hardened amine-catalysed resins or resin dust in minute quantities would not constitute a risk to the consumer. The toxicology of epoxy resins is reviewed by Hine *et al.*[1]

REFERENCE

[1] Hine, C. H., Kodama, J. K., Anderson, H. H., Simonson, D. W., and Wellington, J. S., *A.M.A. Arch. industr. Hlth.*, 1958, **17**, 129.

Gynaecomastia

Q.—*Would hormone treatment help a boy of 17 with bilateral gynaecomastia? He appears healthy, with normal male external genitalia and hair distribution.*

A.—Bilateral gynaecomastia in slight degree may be described as a normal accompaniment of puberty and adolescence, which usually disappears spontaneously during adolescence. It is unusual to find high values for oestrogens in the urine in such cases, so that the mechanism is not obvious, although gynaecomastia may be associated with adrenal hyperfunction involving the glucocorticoids. Very rarely this is associated with an adrenal tumour. The administration of hormones, such as androgens, does not appear to influence the condition. If, therefore, the gynaecomastia is prominent and persistent, plastic surgery should be undertaken. The modern technique with peri-areolar incision gives an excellent cosmetic result without an obvious scar.

Treatment of Diverticulitis

Q.—*What is the treatment of diverticulitis between acute episodes?*

A.—It is desirable for the patient to pass an easy bowel action daily, but to-day there is less insistence on a strict low-residue diet than formerly. Indeed, without residue in the diet individuals tend to become constipated. In practice it is better for them to continue with greens and salads. At the same time, it is reasonable to avoid any particularly rough stalky vegetables, pips, and skins, and root vegetables which tend to produce wind. These patients are rather sensitive to wind discomfort. If dietetic treatment alone is insufficient to provide an easy stool they should then be given a mild laxative which would not cause griping. Phenolphthalein gr. 1–2 can be very satisfactory. A few patients occasionally find regular washouts helpful, but there is little really to commend them. Antibiotics should be reserved for any acute exacerbation.

Tongue-biting During Sleep

Q.—*A man who wears a partial denture bites his tongue in his sleep. His incisors are his own. Would some sort of rubber gag or gum-shield help him?*

A.—It is difficult to answer this question without further knowledge of the circumstances. For example, a denture which does not fit particularly well may cause irritation which results in involuntary movements of the jaw during sleep. Secondly, patients who have their own incisor teeth but no teeth posteriorly, and who leave their dentures out at night, may suffer from some overclosure, owing to the absence of molars on which to bite, and may bite their

tongue as a result. If the patient bites his tongue whether he wears partial dentures at night or not, it might be worth trying a small rubber gag. If this is done, however, care must be taken that a device is attached, or a flange of sufficient size fitted, to prevent any possibility of swallowing it. A frequent cause of irritation in the mouth of patients with their own incisors but no posterior teeth is a slight hingeing action owing to the back of the denture falling down, and attention to the denture may assist.

Interlocking Inoculations

Q.—*Is there any disadvantage in interlocking poliomyelitis and diphtheria inoculations — e.g., one for poliomyelitis followed by one for diphtheria in 2–4 weeks, and so on?*

A.—There is no disadvantage, either from the point of view of reactions or from the immunity produced, if these inoculations are interlocked.

Treatment of Neuropathic Keratopathy

Q.—*What is the treatment of neuropathic keratitis after alcoholic injection of the Gasserian ganglion?*

A.—The treatment of neuropathic keratitis (more correctly described as neuropathic keratopathy) consists in (1) simple preventive measures, and (2) more drastic methods necessary when there are signs of early pathological change in the cornea.

The simple preventive measures include the wearing of a pair of glasses with protective sides, or, better still, a specially constructed transparent eye-shield which excludes all air from the eyeball. In addition, "paroleine" eye drops should be used several times throughout the day. The danger of serious involvement of the cornea is considerably reduced if the treatment is carried out efficiently for the first four or five weeks after alcohol injection of the Gasserian ganglion.

Tarsorrhaphy should be undertaken without delay if there are signs of involvement of the cornea, and the eyelid should remain closed for a period of at least six months and sometimes up to one year. The tarsorrhaphy need not be complete, but it should give coverage to the affected part of the cornea.

Eventually the corneal tissues appear to become adjusted to the new condition of metabolism, and if precautions are taken against trauma and exposure to dust and cold winds the affected eye may eventually keep well. In intractable cases the wearing of a contact lens may spare the patient a permanent tarsorrhaphy.

Vaginal Specimens for Cytological Examination

Q.—*What is the best method of obtaining a specimen of vaginal mucous membrane for cytological examination and diagnosis of a patient's endocrine state?*

A.—Hormonal diagnosis, based on vaginal cytology, makes use of exfoliated vaginal cells rather than biopsy specimens from the vaginal wall. To obtain the vaginal cells either a glass tube with a rubber bulb attached, whereby secretions from the upper third of the vagina may be aspirated, or a cotton-wool applicator on a stick may be used. Advocates of the aspiration method claim that its use preserves the distinct arrangement of cells, if one exists (e.g., clumping in the progestational phase), which the use of a cotton-wool applicator may fail to do. This point, however, is disputable, provided the cotton-wool applicator, after insertion into the vagina, is then *rolled* rather than rubbed on to a glass slide. By the aspiration method the secretions are squirted on to the slide. For detailed cytological study the preparation must not be allowed to dry but must be fixed immediately in equal parts of absolute alcohol and ether. The slides may remain in the fixative for many days or may be stained within two hours. For determination of the pyknotic index, however, and for less detailed study, allowing the slides to dry before fixation, contrary to what has often been stated, does not prevent satisfactory diagnosis by vaginal cytology. For cancer detection immediate fixation is essential. For a detailed exposition of diagnosis by vaginal cytology the reader is referred to the book by de Allende and Orias.[1]

REFERENCE

1 de Allende, I. L. C., and Orias, O., *Cytology of the Human Vagina*. 1950. Hoeber, New York.

Chiari–Frommel Syndrome

Q.—*What is the most appropriate form of replacement therapy in the so-called Chiari–Frommel syndrome (galactorrhoea, amenorrhoea, loss of libido, and loss of weight with evidence of uterine-ovarian atrophy)? The patient has an excessive production of pituitary gonadotrophins accompanied by a paucity of gonadal hormones.*

A.—In the Chiari–Frommell syndrome there is under- not over-production of pituitary gonadotrophins, with the exception, it is generally believed, of prolactin. There is no really effective treatment for the condition, though with cyclic oestrogen and progestogen therapy uterine growth and withdrawal bleedings can be induced. Treatment with norsteroid progestogens, either norethisterone ("primolut N"[1]) or norethynodrel ("enavid") might be tried. The steroid could be given either cyclically in a dose of 10–20 mg. daily for 20 days, repeating from the fifth day of each subsequent withdrawal bleeding, for perhaps six cycles in the first instance, or continuously, starting at 10 mg. daily and increasing by 10 mg. a day every two weeks until 40 mg. daily is reached, for, say, six months so as to produce a "pseudopregnancy." It is possible, though certainly not probable, that normal menstruation might then be resumed.

REFERENCE

1 "To-day's Drugs," *Brit. med. J.*, 1958, **1**, 1297.

Melanin in Substantia Nigra

Q.—*Is the pigment of the substantia nigra melanin? A patient with a recent Parkinson syndrome has developed more recently evidence of metastatic melanoma. Is this associated in any conceivable way?*

A.—The pigment in the substantia nigra is considered to be melanin. The development of metastatic melanoma in a patient with a "recent Parkinson syndrome" is interesting, but it is difficult to suggest a direct association between the two conditions.

Correction.—In the summary of Dr. J. P. Bound's paper read at the Joint Annual Meeting (*Journal*, September 12, p. 424) it is stated that Dr. Bound comes from Liverpool. In fact, he comes from Blackpool.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.).

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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